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Archives of Neurology and Psychiatry

VOLUME 70 DECEMBER 1953 NUMBER 6

HIPPOCAMPAL SEIZURES AND THEIR PROPAGATION

J. D. GREEN, D.M. (Oxon.), B.M., B.Ch.
AND
T. SHIMAMOTO, M.D.
LOS ANGELES

STIMULATION of various parts of the rhinencephalon is known to produce seizure-like electrical after-discharges in the cerebral cortex. Kaada [1] has recently explored this subject at length and reviewed the pertinent literature. In recent studies [2] it has been shown that stimulation of the dorsal fornix and the fimbria hippocampi in the guinea pig and cat leads to cerebral and cerebellar after-discharges. Although they appear to spread over neural pathways and can be induced by stimulation of the fibers of the fimbria alone,[2c] the precise routes involved are not yet clear, and the possible role of volume conduction in their propagation is not yet settled. The participation of subcortical structures, as well as their importance in the maintenance of the after-discharges, is also a matter requiring further study. Finally, the effects of stimulation of the fimbria in unanesthetized and unparalyzed animals is of interest, for, although Penfield and Erickson [3] found that stimulation of the hippocampus produced no motor response in humans, recent studies by Kaada and Jasper [4] indicated that a grand-mal type of seizures could be induced, and Hunter [5] observed petit-mal-like effects in conscious cats when the general region of the fornix was stimulated. This study is an attempt to elucidate these problems.

John and Mary R. Markle Scholar in Medical Science (Dr. Green).

Visiting Investigator, University of Tokyo, Tokyo, Japan (T. Shimamoto).

Aided by a grant from the National Institute of Neurological Diseases and Blindness, United States Public Health Service.

From the Department of Anatomy, University of California School of Medicine at Los Angeles, and the Investigative Medicine Service, Veterans Administration Hospital, Long Beach, Calif.

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2. (*a*) Green, J. D., and Morin, F.: Observations on the Electrical Activity of the Hypothalamus, Anat. Rec. **112**:335, 1952; (*b*) Hypothalamic Electrical Activity and Hypothalamocortical Relationships, Am. J. Physiol. **172**:175-186, 1953. (*c*) Morin, F., and Green, J. D.: Diffuse After-Discharges Following Stimulation of the Fimbria Hippocampi, to be published.

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MATERIALS AND METHODS

Forty-two cats were used. In all but two cases experiments were carried out on curarized animals after recovery from preliminary ether anesthesia. Both tubocurarine and decamethonium (Syncurine) were used. Local procaine infiltration was carried out in all areas likely to be painful. The fimbria hippocampi was exposed by suction and was usually stimulated by coaxial electrodes applied directly to it. In three animals the fimbria was dissected free from underlying tissues and stimulated in liquid petrolatum U. S. P. with only one end in continuity with the brain. Records were obtained with a Grass eight-channel electroencephalograph. Subcortical recordings were obtained with coaxial electrodes oriented by means of a stereotaxic machine. Stimulation was by means of condenser discharges with a falling phase of 1 msec., usually at a frequency of 50 a second. Thresholds were determined at stimulus durations of 10 seconds and corresponded with those previously reported for square-wave stimulation (0.5 to 1.0 volt), an occasional animal being somewhat more sensitive (0.1 volt). While a variety of stimuli were used and the pulse length, frequency, and duration varied from time to time, the usual stimulus was a train of 1-msec. pulses at 5 volts for 10 seconds.

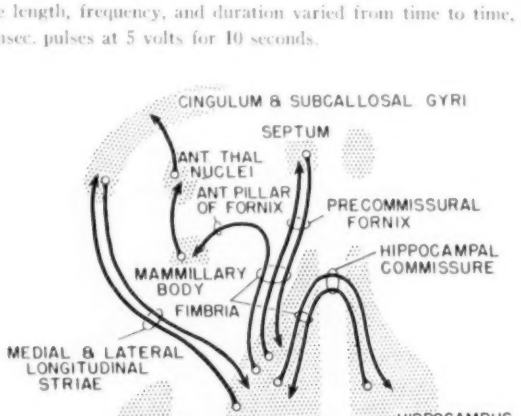

Fig. 1.—Diagram of some of the known connections of the hippocampus.

Anatomical Considerations.—In the fimbria there are three groups of fibers: (1) those which pass forward to the septum as the precommissural fornix, which probably includes both afferent and efferent connections; (2) those passing into the fornix proper, presumed to be entirely efferent from the hippocampus, and (3) commissural fibers, which presumably interconnect the hippocampi. The hippocampus receives fibers from the pyriform cortex and other rhinencephalic structures and may also send efferent fibers to them, although this is not entirely clear in higher animals. Through the fornix and mammillary body the hippocampus is connected with the anterior thalamic nuclei and (via the mammillotegmental tract) with the midbrain tegmentum. There are also other connections of the mammillary body with the brain stem, both of an afferent and of an efferent nature; and it is said that the fornix gives rise to collaterals to hypothalamic structures other than the mammillary body. Some of the connections are summarized in Figure 1.

RESULTS

General Characteristics—Subcortical Recording; Volume Conduction.—The general nature of hippocampal after-discharges is shown in Figures 2, 3, and 4. When the strength of the stimulus is small (Figs. 3 and 4), the activity is confined

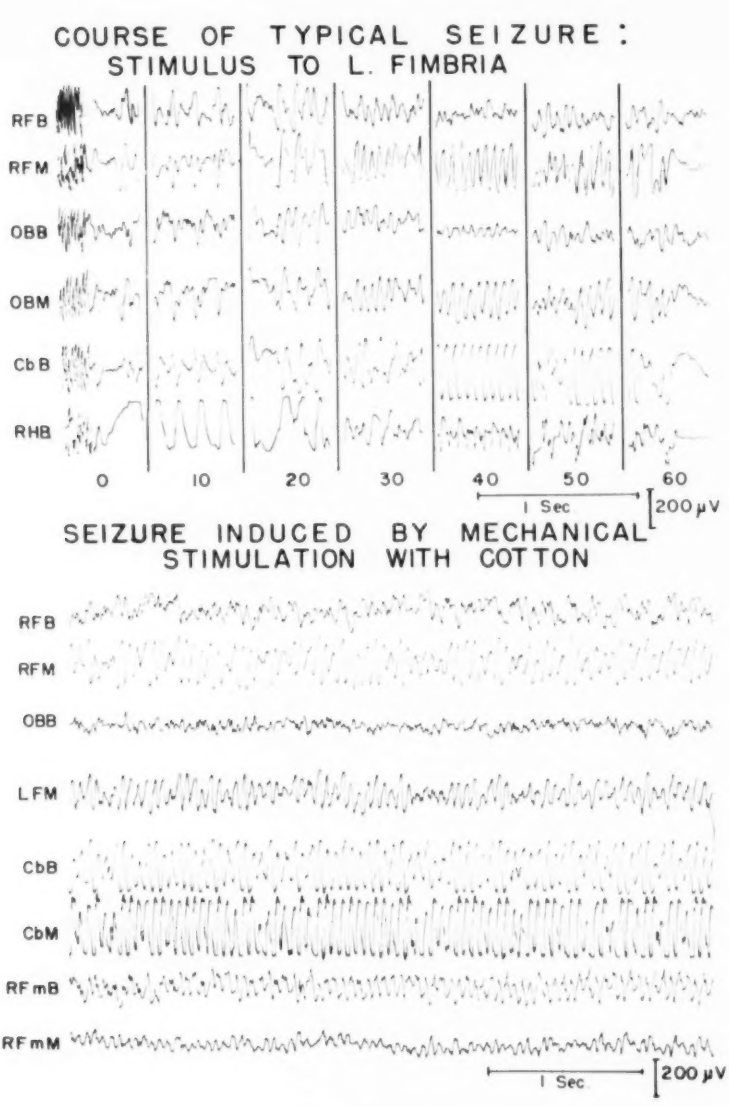

Fig. 2.—The first record shows the course of a typical seizure discharge produced by electrical stimulation of the fimbria hippocampi. The figures at the bottom in this record, and in subsequent records, indicate the number of seconds from the end of stimulation. Note that changes in frequency, amplitude, and time relationships differ from area to area and at different times in the course of the discharge.

The second record shows part of a discharge induced by mechanical stimulation (stroking the fimbria with a pledget of cotton).

Leads: *RFB*, right frontal, bipolar; *RFM*, right frontal, monopolar; *OBB*, olfactory bulb, bipolar; *OBM*, olfactory bulb, monopolar; *CbM*, cerebellum, monopolar; *CbB*, cerebellum, bipolar; *RHB*, right hippocampus, bipolar; *LFM*, left frontal, monopolar; *RFmB*, right fimbria, bipolar; *RFmM*, right fimbria, monopolar.

to the hippocampal formation and its immediate projections; when stronger, it is seen in all parts of the cerebral and cerebellar cortex, and can be obtained from a variety of subcortical structures also. The onset may be quite localized, as it usually is when the hippocampus is simply punctured by a recording electrode, and then often has a frequency of 30-45/sec. After a few seconds this discharge spreads to adjacent regions on the same side or to the opposite hippocampus. The magnitude of the discharges now has a tendency to wax and wane and, if the stimulus is sufficiently weak, may gradually die out without any sign of an abrupt termination. Sometimes there is a tendency for first one hippocampal area to discharge

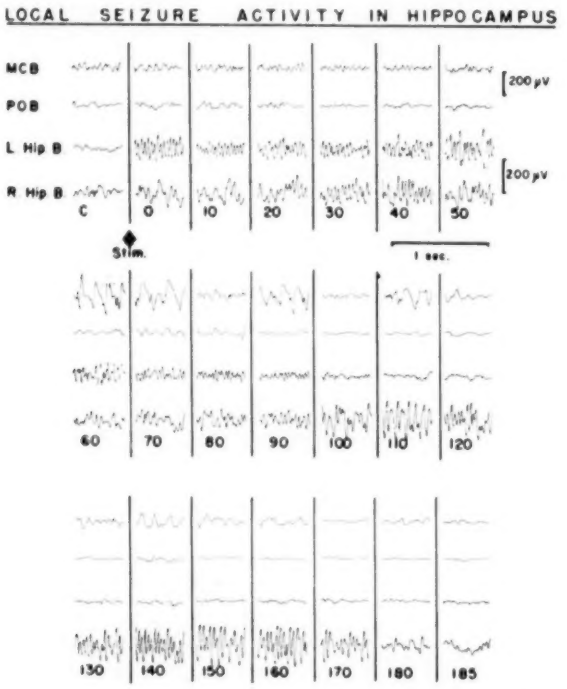

Fig. 3.—Example of a localized discharge induced by stimulation of the left fimbria in a curarized animal (2 volts, 50/sec., 5 seconds). Note the rapid onset in the left hippocampus, the delayed appearance (at 60 seconds after end of stimulus) in the cortex, and the spread to the right hippocampus, which continues to discharge after other areas have become quiescent.

Leads: *MCB*, motor cortex, bipolar; *POB*, parieto-occipital; *L. Hip. B.*, left hippocampus (coaxial); *R. Hip. B.*, right hippocampus (coaxial).

and then another. If the stimulus is a little greater, the hippocampus may suddenly change its rate of discharge to from 18 to 22 a second, and this usually heralds spread to adjacent regions, even to the rest of the brain. In Figure 2, a generalized discharge following mechanical stimulation of the fimbria is seen. The onset of hippocampal after-discharges after electrical stimulation of the fimbria is difficult to see, since they are partially obscured by the shock artifact. Consequently, the impression of an abrupt onset is gained. Since this form of stimulation is most readily controlled, exploration of the brain stem for signs of after-discharges was

carried out after electrical stimulation, and this probably accounts for the lack of evidence for an area-to-area spread in these studies. After-discharges were, in fact, recorded from most areas of the basal ganglia, thalamus, hypothalamus, midbrain tegmentum, internal capsule, and cerebral peduncles, but were almost always diffuse in nature. An example of an after-discharge in the thalamus is shown in Figure 5. In some cases the after-discharges merge into a so-called jack-in-a-box discharge, or this may succeed a hippocampal after-discharge after a few seconds. These are, apparently, more synchronized than the typical hippocampal after-dis-

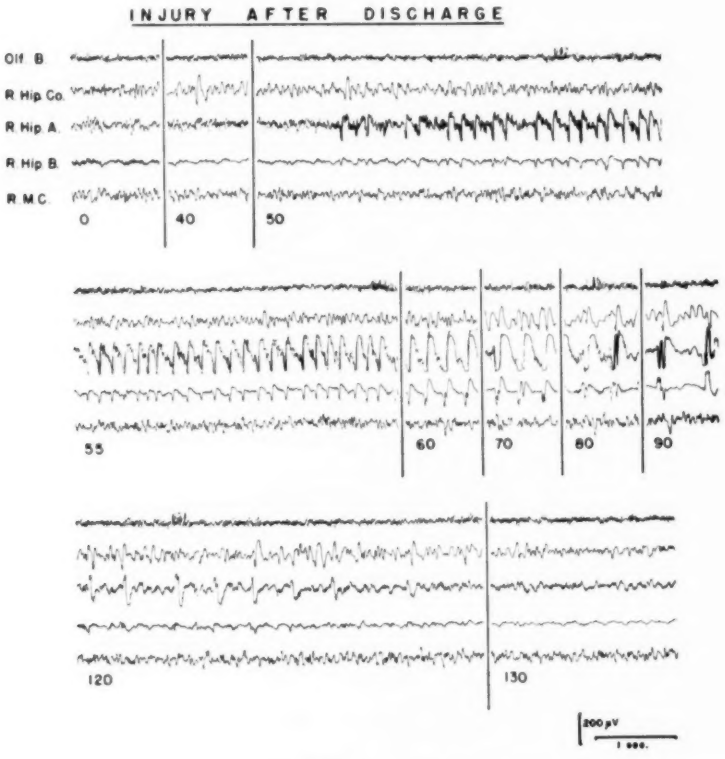

Fig. 4.—Example of a hippocampal discharge appearing shortly after the structure was punctured by recording electrodes. Note isolated spikes at 40 seconds, gradual appearance of discharge in middle hippocampal lead and occasional low-amplitude synchronous waves in the motor cortex (at 60 to 90 seconds).

Leads: *Olf. B.*, olfactory bulb; *R. Hip. Co.*, hippocampal commissure at right; *R. Hip. A.*, right hippocampus (middle lead); *R. Hip. B.*, right hippocampus (posterior lead); *RMC*, right motor cortex.

charge and, apparently, more generalized. The termination of the hippocampal and jack-in-a-box type of after-discharges is abrupt except when synchronous activity is confined to the hippocampus itself, in which case a gradual diminution in amplitude occurs and the discharge gradually fades away. An isoelectric period does not normally follow a hippocampal after-discharge under these conditions.

One other characteristic of the hippocampal discharges should be mentioned because of a certain similarity to psychomotor fits. Often after a puncture has been made in the hippocampus, isolated spikes appear in the record, with or without accompanying spikes in the EEG. These may die away or gradually increase in

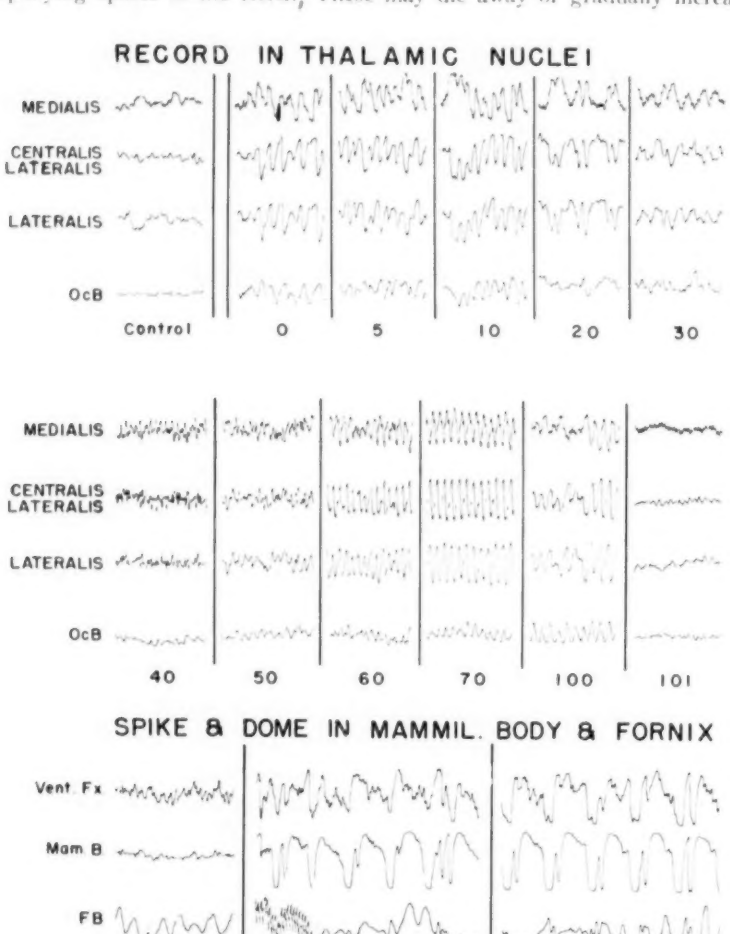

Fig. 5.—In the first record, a discharge is seen following a stimulus of 5 volts, 50/sec. for 10 seconds, to the left fimbria. An active thalamic discharge is seen. This is continued in the next record, where the appearance of a "jack-in-a-box" discharge is observed. In the last record a control strip is seen, followed by a spike-and-dome discharge in the region of the ventral fornix and the mammillary body. This is not a contrast type of discharge, however (see Figure 7).

Leads: *OcB*, occipital, bipolar; *FB*, right frontal cortex, bipolar; *Vent. Fx.*, ventral fornix; *Mam. B.*, mammillary body.

frequency and amplitude until a typical generalized discharge occurs. When the strength of stimulus is large or its duration prolonged, slower components also appear in the records. These waves range from 3 to 10/sec. and an example is seen in the hippocampal lead in Figure 3.

Application of strychnine to the hippocampus at first lowered the threshold for the induction of after-discharges and greatly increased their duration. In one case

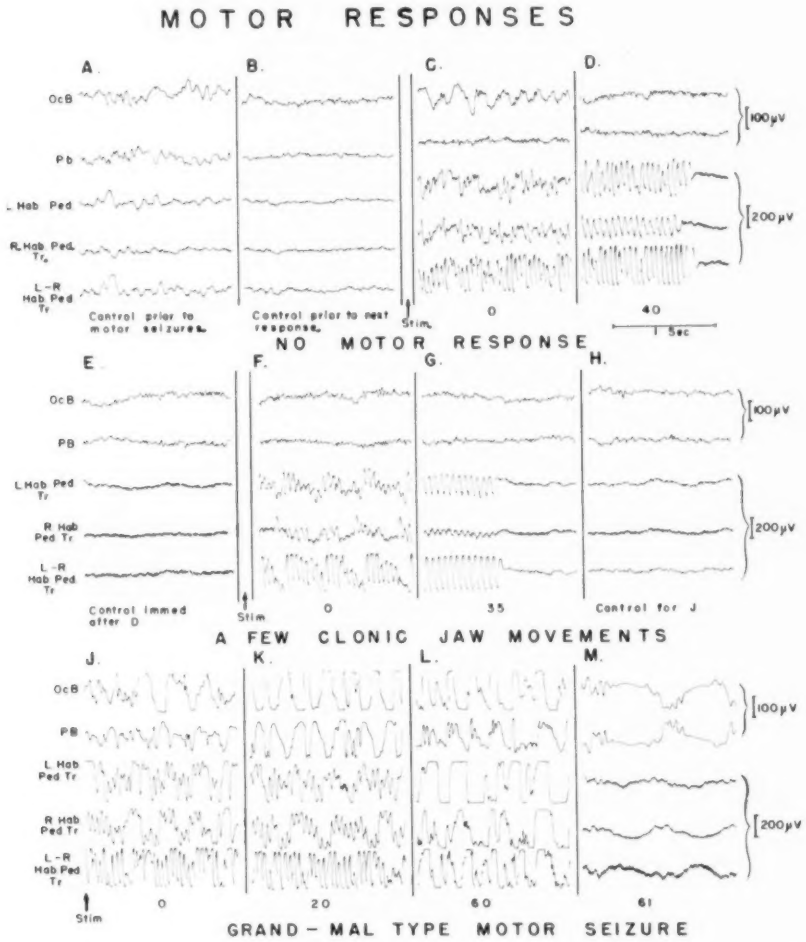

Fig. 6.—Electrical activity in an animal which showed marked motor responses after recovery from Syncurine. Examples of activity accompanied and not accompanied by motor activity. *B-D*, discharge following subthreshold stimulus, without motor effect; *E-G*, threshold stimulus accompanied by a few clonic jaw movements; *H*, control prior to *J*; *J-M*, larger stimulus inducing a grandmal type of fit, with tonic and clonic phases, urination defecation, salivation, dilated pupils, and staring facies. Several seizures were induced between *A* and *B*, and in all six motor fits were obtained within 30 minutes.

Leads: *OcB*, occipital, bipolar; *PB*, parietal, bipolar; *Hab-Ped Tr.*, habenulopeduncular tract.

(in which, however, there were some strychnine waves in the cerebral cortex) stimulation of the fimbria induced an after-discharge which lasted over four hours and was still occurring with undiminished vigor when the animal was killed. As indicated previously,[2c] pentobarbital (Nembutal) has a contrary action and greatly diminishes the duration or abolishes the after-discharges.

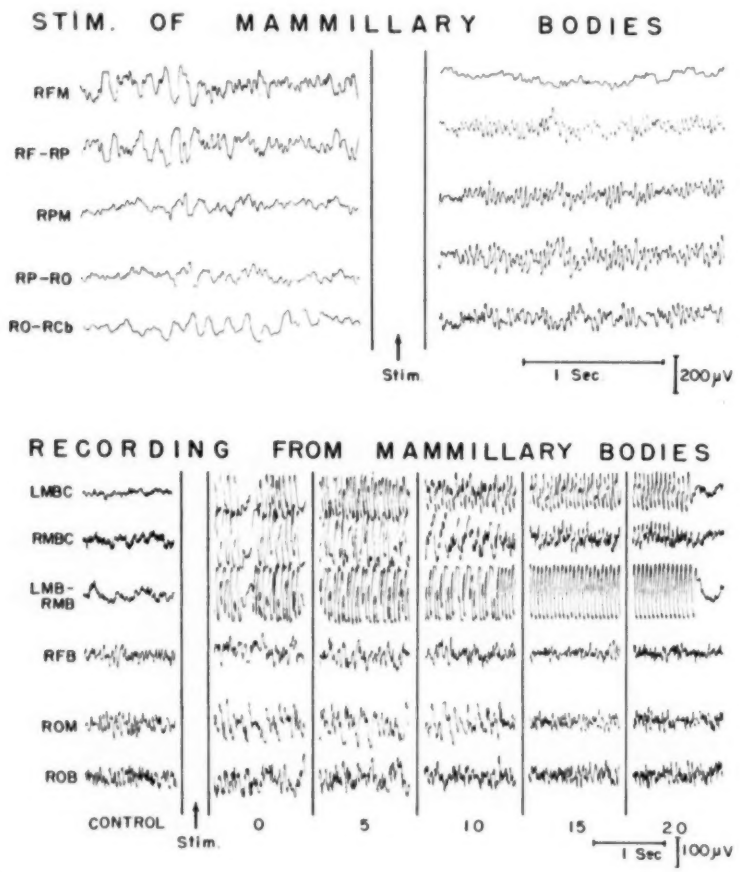

Fig. 7.—In the first records it can be seen that stimulation of the mammillary body evokes a fast discharge of high amplitude but of characteristics differing from those of the usual hippocampal discharge. On the other hand, as seen in the lower record, very marked activity can be recorded from the mammillary body during the course of a discharge.

Leads: *RFM*, right frontal, monopolar; *RF-RP*, right frontal to right occipital; *RPM*, right parietal, monopolar; *RP-RO*, right parietal-right occipital; *RO-RCb*, right occipital-right cerebellar; *LMBC*, left mammillary body, coaxial; *RMBC*, right mammillary body, coaxial; *LMB-RMB*, left mammillary body to right; *RFB*, right frontal, bipolar; *ROM*, right occipital, monopolar; *ROB*, right occipital, bipolar.

Presumably the widespread activity of these discharges, occurring throughout the brain, involves a considerable current as well as voltage change. It might be

predicted, therefore, that voltage changes could be detected at sites far distant from the source of activity. Such appeared to be the case, since it was found [2b] that the after-discharges could be recorded with ease from the surface of the cerebral or cerebellar cortices after they had been completely coagulated with silver nitrate. Figure 1 shows that volume conduction does in fact play a part, for there is a considerable difference in the activity of the monopolar and the bipolar leads. Nevertheless, it also shows that some degree of localization is possible, and this is evident from a comparison of the activities in the cerebellar and hippocampal leads, the hippocampus being highly synchronized at the beginning of the after-discharge and much less so at its termination, while the cerebellar activity shows the reverse changes. Furthermore, it may be seen from the records presented that (1) it is possible to have activity localized to the hippocampus and its projections (Figs. 3 and 4) and (2) that there are phase, as well as amplitude, differences between various leads (Fig. 2).

Motor Effects Following Stimulation of the Fimbria.—In four cats motor fits were observed in the course of experiments during which the paralyzing effect of the curare wore off. These fits usually required a stronger stimulus than was necessary to excite an after-discharge in the cerebral cortex. Nevertheless, they could be induced at low threshold. In the case of one rabbit in which bipolar electrodes were implanted in the hippocampus and stimulation was carried out five days later, several motor fits were elicited and a threshold was roughly determined at 100 mv and 50 a second for less than two seconds. In cats these fits were of the grand-mal type, with an initial tonic phase, followed by clonic movements. The pupils were widely dilated, and the animals urinated and defecated. In the case illustrated, six such seizures were induced within the space of a little more than an hour. An isoelectric phase succeeded the motor fits, though it was not usually seen after a hippocampal after-discharge in a curarized animal. An example of electrical activity during a motor fit is seen in Figure 6.

Structures Involved in the Initiation, Maintenance and Propagation of Hippocampal After-Discharges.—In order to verify once more the selective excitability of the fimbria, this structure was partially dissected from the hippocampus in three animals and stimulated in a pool of liquid petrolatum. As found previously,[2c] this procedure still produced after-discharges. Since mechanical stimulation of the fimbria by means of a wisp of cotton or by pricking with a sharp needle also produces the same pattern of activity, it is concluded that selective stimulation of the fimbria alone is enough to initiate typical after-discharges.

In earlier experiments [2] there was an apparent contradiction in that seizure discharges could be induced in the guinea pig by stimulation of any part of the fornix, while, on the other hand, the effect was not abolished by interruption of the fornix anterior to a point of stimulation in the hippocampal commissure. The possible explanations for these findings might be (1) stimulus spread when stimulation was done in the hypothalamus, (2) antidromic synchronization of the hippocampus, (3) inadvertent damage to the thalamus by the sections (made with a diathermy knife), or (4) the presence of two excitable areas. It was decided, therefore, to repeat these experiments in the larger brain of the cat and to cut the fornix with an ordinary knife rather than with the diathermy.

The mammillary body and ventral fornix were stimulated on several occasions with concentric electrodes. In no cases were the typical after-discharges seen, though high-amplitude activity was seen in the cortex (Fig. 7). Both fornices were cut in five animals near the foramen of Monro, after this area had been exposed by suction. In order to test the possibility that the diencephalic fornix played a role

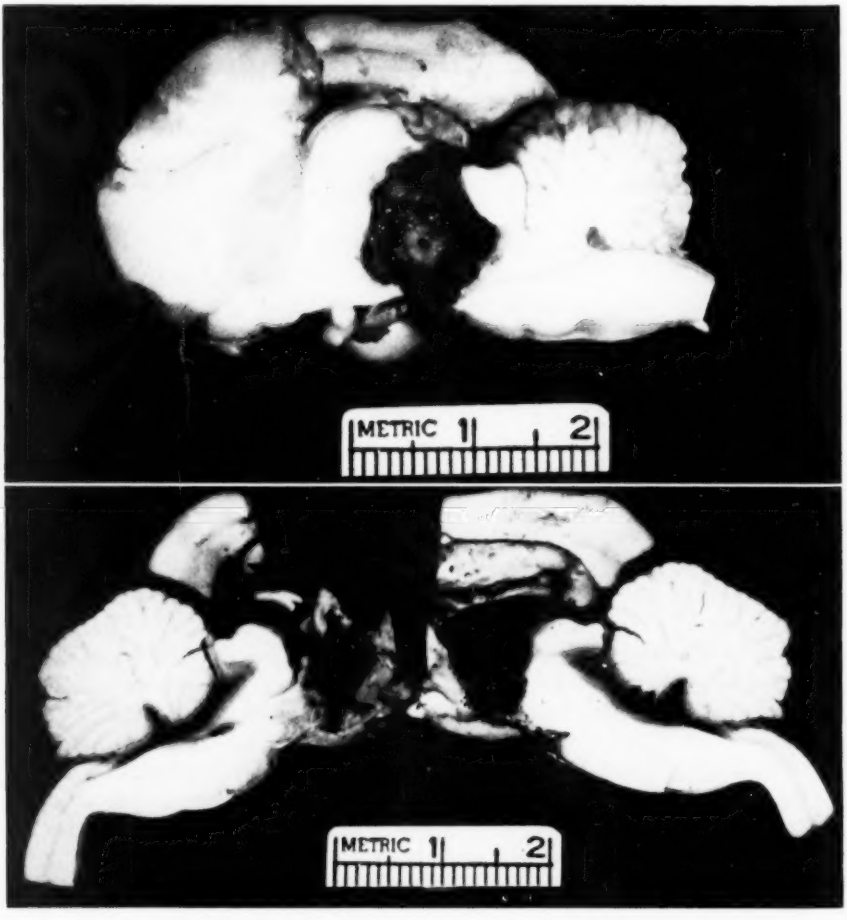

Fig. 8.—Photographs of the brains of two cats in which most of the thalmas and hypothalamus was destroyed by suction. In both cases stimulation of the fimbria still evoked generalized discharge in the cortex (see Figure 9 for example). In the first case the posterior thalamus was destroyed, the midbrain completely transected, and the greater part of the hypothalamus removed. In the second, the pipette was introduced by sucking out the anterior pillars of the fornix, and the anterior thalamus and hypothalamus were completely destroyed.

in the propagation of these seizure discharges, the bulk of the thalamus was removed by suction in two animals. In both cases destruction was extensive. The brains are shown in the photographs (Fig. 8). In the first case, that of destruction of the

posterior thalamus, most of the midbrain tegmentum and a large part of the hypothalamus were removed. The midbrain was completely severed, and only a thin shell of the ventral part of the mammillary body was undamaged. Apparently the ventral fornix and mammillothalamic tracts were completely interrupted. In the second case the tip of the suction pipette was inserted through a hole made by

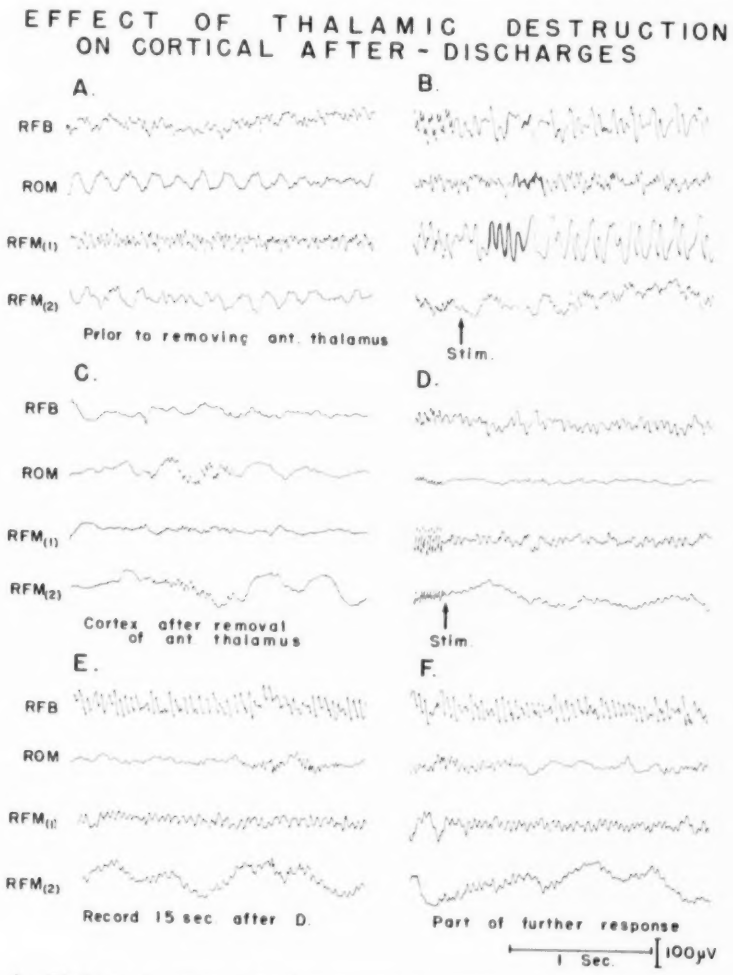

Fig. 9.—Discharge in cortex following removal of anterior thalamus and stimulation of fimbria (second animal of Figure 8).

Leads: *RFB*, right frontal, bipolar; *ROM*, right occipital, monopolar; *RFM (1)*, right frontal (*1*), monopolar; *RFM (2)*, right frontal (*2*), monopolar.

sucking out the anterior pillars of the fornix. The anterior two-thirds of the thalamus was completely removed, and the bulk of the hypothalamus, including the mammillary bodies, also destroyed by suction. In spite of the shock induced by

this extensive lesion, seizure-like after-discharges could still be recorded from the cerebral cortex (Fig. 9). It must be concluded, therefore, that the diencephalon is not necessary for the appearance, maintenance, or propagation of these after-discharges. It seems, therefore, that only the dorsal fornix (including precommis-

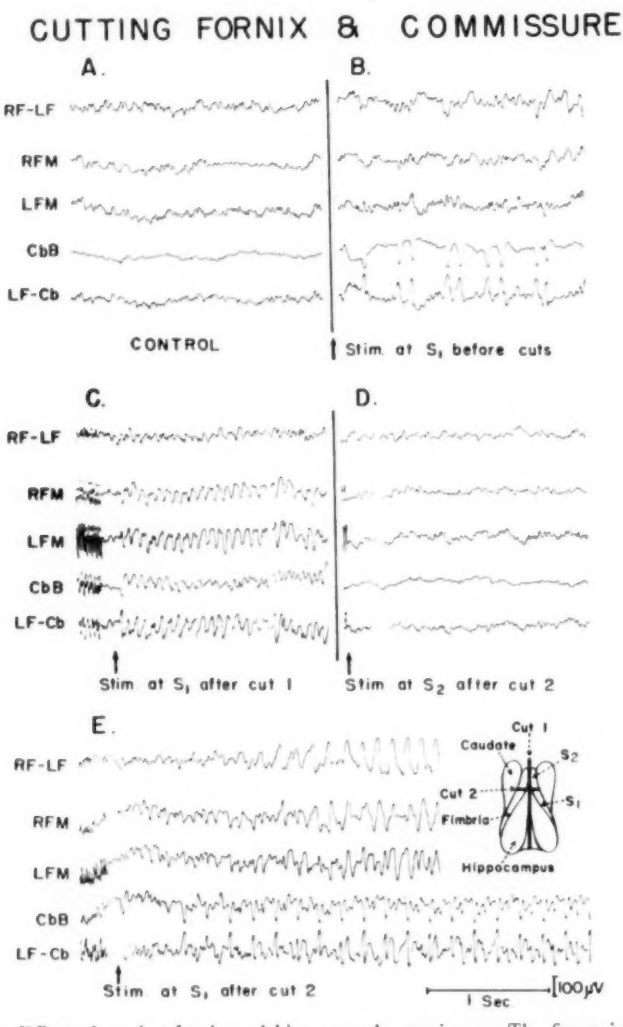

Fig. 10.—Effect of cutting fornix and hippocampal commissure. The figure is self-explanatory. The small diagram indicates the structures visualized by suction dissection.

Leads: *RF-LF*, right frontal-left frontal; *RFM*, right frontal, monopolar; *LFM*, left frontal, monopolar; *CbB*, cerebellum, bipolar; *LF-Cb*, left frontal-cerebellum.

sural fibers and some commissural fibers), the fimbria proper, and the hippocampus itself can initiate after-discharges when this region is stimulated. Stimulation of other parts of the rhinencephalon, particularly in the region of the uncus and pyri-

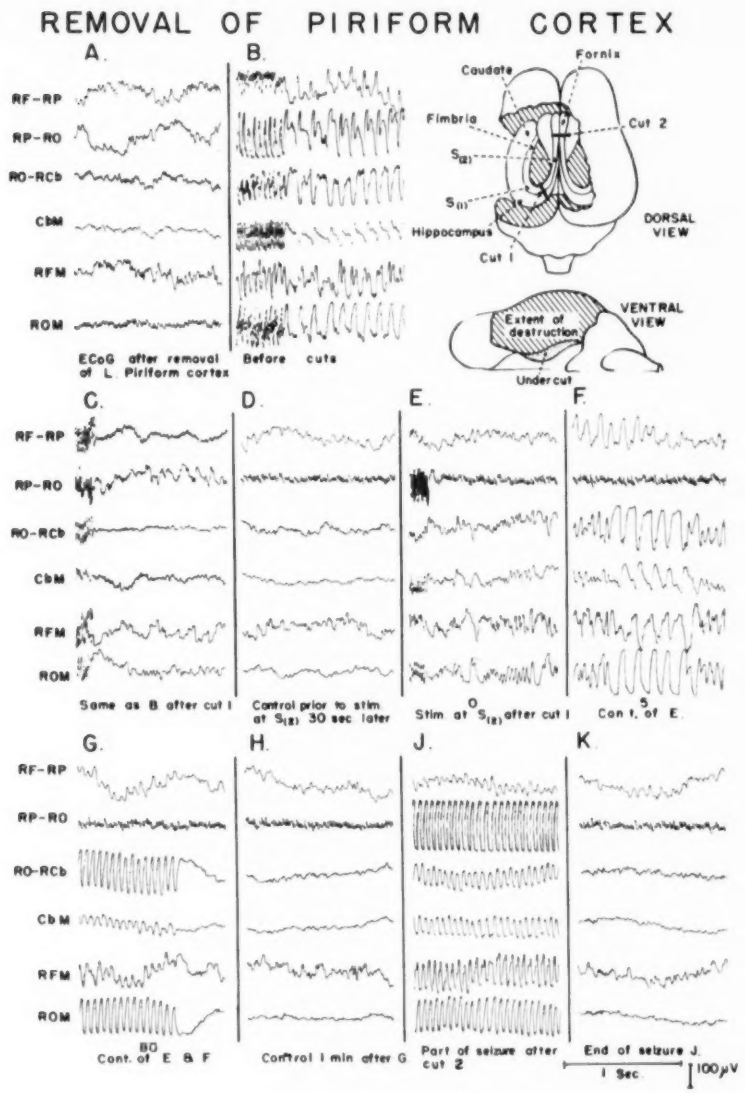

Fig. 11.—Experiment designed to test the significance of the temporal lobe and pyriform cortex in the propagation of seizure discharges induced by stimulating the fimbria hippocampi. The figure is self-explanatory, and the results indicate that the area of the fimbria stimulated must be connected to one or the other temporal lobe through the fibers of the hippocampal commissure for the development of the typical discharge but that connections to the thalamus by way of the fornix are not essential.

Leads: *RF-RP*, right frontal-right parietal; *RP-RO*, right parietal-right occipital; *RO-RCb*, right occipital-right cerebellum; *CbM*, cerebellum, monopolar; *RFM*, right frontal, monopolar; *ROM*, right occipital, monopolar.

form cortex, can produce similar after-discharges, and in these experiments the excitable regions appeared to confirm earlier observations (Kaada,[1] 1951).

Since the rostral connections of the hippocampus with the fornix and mammillary body are not essential and their destruction does not prevent the after-discharges, projection from the hippocampus into the pyriform cortex or temporal lobe must be postulated.

The hippocampal discharges are recorded equally well in the two hemispheres. Exposure of the dorsal hippocampi destroys the greater part of the corpus callosum. Even if the whole of this structure is destroyed, they persist. This excludes also the necessity for cingulate gyrus and cingulum. Destruction of the diencephalon also involves destruction of the anterior commissure, the habenular commissure, the posterior commissure, and the massa intermedia. Since hippocampal after-discharges are still bilateral under these conditions, they can, presumably, spread to the contralateral hemisphere through the hippocampal commissure. This cannot be the only means of spread, however, since section of the hippocampal commissure after destruction of the corpus callosum does not prevent bilateral after-discharges. In order that the effects of sections and dissections of the fornix and hippocampal commissure may be clarified, these procedures are summarized in the diagram in Figure 10.

Section of the hippocampal commissure does not exclude the possibility that commissural fibers are involved in the propagation of the hippocampal after-discharge, since within the commissure there are fibers passing in both directions. Thus, after section of the commissure, stimulation of the fimbria could lead to activity in the ipsilateral side, which could then pass to the contralateral side through some commissural connection other than the hippocampal commissure. It does, however, exclude any possibility of a reverberating circuit between the two hippocampi as an essential part of the hippocampal seizure. By a process of exclusion, therefore, it seems that (1) caudally running connections of the fimbria must be involved, (2) these cannot be derived from the fornix or from septohippocampal fibers, and (3) the only likely remaining connection lies in the hippocampal commissure, which cannot so far be excluded. Presumably, connections would have to exist between the hippocampus and pyriform cortex or temporal lobe. To test this last possibility, the following experiment was devised and carried out in two animals, with essentially the same findings in the two. The whole extent of the left hippocampus and a part of the dorsal aspect of the right hippocampus were exposed by suction of structures overlying the lateral ventricles. The left pyriform cortex and temporal lobe were then removed by suction until only a thin medial remnant, about 2 mm. wide, remained. This was severed from the rest of the brain by undercutting. The whole of the temporal lobe, except the hippocampus, was removed. Stimulation of the ventral part of the left fimbria was carried out, and a typical after-discharge was recorded. The hippocampus and fimbria were then severed by a very small cut just behind the hippocampal commissure. All parts of the hippocampus below this point were thus cut off from connections with the opposite hippocampus, and no after-discharge could then be evoked by stimulation of the ventral fimbria or hippocampus. In order to see whether the hippocampus was still viable, stimulation was applied just rostral to the cut. A typical seizure discharge could be evoked repeatedly. Presumably, this was due to conduction across the hippocampal commis-

sure to the opposite side. Finally, the fornices were again transected rostrodorsally. Stimulation between the two cuts still evoked the same kind of after-discharge. These results are shown in Figure 11.

COMMENT

These experiments do not, of course, exclude the possibility of alternative routes of propagation of hippocampal after-discharges. They do, however, show that they can pass across the hippocampal commissure and into the pyriform area and seem to indicate that they are not propagated through the fornix and mammillary body to the thalamus and cerebral cortex, as might be expected a priori. Certainly the after-discharges recorded from the cerebral cortex cannot be entirely due to corticothalamic reverberating circuits, since removal of the thalamus does not prevent them. Indeed, the extent and variety of lesions which can be inflicted on the brain without preventing their appearance lends support to the contention of Moruzzi [6] that the reverberating-circuit hypothesis for seizure discharges can only be sustained by a variety of subsidiary hypotheses, in particular by assuming that these circuits exist for the most part in very localized areas or on a microscopic scale. At all events, corticothalamic or hippocampohippocampal reverberating circuits, whether or not they exist during the after-discharges, can be positively excluded as a necessary feature. Indeed, since the hippocampus, like many other parts of the brain, can sustain a localized seizure-like after-discharge, the site of activity itself would have to constitute the reverberating circuit.

Since localized hippocampal discharges slowly decrease in amplitude and die away at different times in different parts of the hippocampus, while generalized discharges end abruptly, or at all events synchronously, any arresting mechanism which terminates the diffuse hippocampal and cortical activity must lie outside the hippocampus. If such a mechanism lies in the nervous system, it must also lie rostral to the midbrain, for the discharges end equally synchronously in *cerveau isolé* preparations. The diencephalon would presumably be the most likely site for any hypothetical suppressor area, and a diffuse termination was seen after removal of the thalamus and hypothalamus.

The low threshold of hippocampal seizures suggests that the hippocampus may be involved in electroshock, as indicated previously.[2c] Recently Liberson and Cadilhac [7] have obtained more direct evidence for this and have made a detailed study of thresholds, wave forms and DC potentials in hippocampal seizures.

It may also be suggested that the hippocampus is involved at least in some cases of psychomotor epilepsy. Maclean and Arellano [8] found evidence of spike foci near the medial surface of the temporal lobe in some cases and, while the results of Stamps [9] and Gibbs [10] indicate that an anterior temporal focus is commoner in cases

6. Moruzzi, G.: L'épilepsie expérimentale, translated into French by M. Renchlin, Paris, Libraire Scientifique, Hermann & Cie, 1950.

7. Liberson, W. T., and Cadilhac, J. G.: Electroshock and Rhinencephalic Seizure States read before the American Psychiatric Association, Los Angeles, May, 1953.

8. Maclean, P. D., and Arellano, Z. A.: Basal Lead Studies in Epileptic Automatisms, Electroencephalog. & Clin. Neurophysiol. **2**:1-16, 1950.

9. Stamps, F., cited by Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, 1951.

10. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Addison-Wesley Press, 1951.

of this type, it should be emphasized that the hippocampus can give rise to large spikes which may spread either by volume conduction or over neural pathways to the temporal region. In some of our animals, isolated spike-like discharges were seen which gradually changed to seizure-like activity bearing at least superficial resemblance to a psychomotor episode.

SUMMARY

Weak electrical or mechanical stimulation of the fimbria hippocampi in cats induces motor fits and electrical discharges with characteristics having some similarity to those of psychomotor epilepsy. These discharges are not propagated through the fornix but spread through the commissural fibers of the psalterium to the temporal lobe and other parts of the cerebrum. The thalamus and hypothalamus are not essential in this propagation.

Miss Cora Rucker and Miss Mary Hiskey gave technical assistance in the preparation of the microscopic slides; Mr. Charles Bridgman made the drawings and lettering, and Mr Timothy Dodge and Mr. Thomas Masterson did the photography.

FIGURE-GROUND DISCRIMINATION AND THE "ABSTRACT ATTITUDE" IN PATIENTS WITH CEREBRAL NEOPLASMS

WILLIAM S. BATTERSBY, Ph.D.
HOWARD P. KRIEGER, M.D.
MAX POLLACK, A.B.
AND
MORRIS B. BENDER, M.D.
NEW YORK

I. THE PROBLEM

THE LITERATURE dealing with intellectual deficits in man following cerebral damage is both extensive and controversial. Defects in "intelligence," [1] "reasoning," [2] "synthesis," [3] "planned administration," [4] "maintenance of set in the face of interference," [5] "imagination," [6] and numerous other abstract categories have been reported. The conclusion usually drawn has been that these defects were uniquely due to lesions in the frontal lobes.[1a] In most instances, however, this conclusion was based upon the study of only a few selected cases. Moreover, the inference that the defects were specific for frontal lobe lesion was not validated empirically, since few patients with lesions elsewhere in the cerebrum have been examined as controls.

From the Department of Neurology, the Mount Sinai Hospital of New York.

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1. (*a*) Fulton, J. F.: Functional Localization in the Frontal Lobes and Cerebellum, Oxford, The Clarendon Press, 1949. (*b*) German, W. J., and Fox, J. C.: Observations Following Unilateral Lobectomies, A. Res. Nerv. & Ment. Dis., Proc. **13**:378, 1934. (*c*) Halstead, W. C.: Preliminary Analysis of Grouping Behavior in Patients with Cerebral Injury by the Method of Equivalent and Non-Equivalent Stimuli, Am. J. Psychiat. **96**:1263, 1940; (*d*) Brain and Intelligence: A Quantitative Study of the Frontal Lobes, Chicago, University of Chicago Press, 1947.

2. Rylander, G.: (*a*) Personality Changes After Operations on the Frontal Lobes, London, Oxford University Press, 1939; (*b*) Mental Changes After Excision of Cerebral Tissue: A Clinical Study of 16 Cases of Resections in the Parietal, Temporal and Occipital Lobes, Acta psychiat et neurol., Supp. 20, 1943.

3. Brickner, R. M.: The Intellectual Functions of the Frontal Lobes, New York, The Macmillan Company, 1936.

4. Penfield, W., and Evans, J.: The Frontal Lobe in Man: A Clinical Study of Maximum Removals, Brain **58**:115, 1935.

5. Malmo, R. B.: Psychological Aspects of Frontal Gyrectomy and Frontal Lobotomy in Mental Patients, A. Res. Nerv. & Ment. Dis. Proc. **27**:537, 1948.

6. Freeman, W., and Watts, J. W.: Psychosurgery: Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders, Springfield, Ill., Charles C Thomas, Publisher, 1951.

The study of a large number of patients, with cerebral lesions in either the pre- or post-Rolandic areas, has produced equivocal results. Goldstein [7] Rylander,[8] and Halstead [10c,d] reported that patients with tumors involving the frontal lobes had the greatest impairment in intellectual ability. Their opinions differed, however, as to the nature of this impairment. Goldstein stated that the inability to pick a figure out of a complex background (figure-ground discrimination) and difficulty in adopting an "abstract attitude" were the basic intellectual disturbances resulting from frontal lobe lesion.[8] Rylander,[2a] on the other hand, concluded that tumors of the frontal lobe produced a defect in "reasoning," while Halstead felt that "biological intelligence" was affected.[10d]

In contrast to these results, Hebb,[9] in his review of the literature, found that no depression in psychometric intelligence had been reported after the removal of frontal lobe tumors. Hebb criticized previous conclusions drawn from the study of patients with cerebral tumors, pointing out that such lesions probably produce widespread brain dysfunction. Therefore, according to Hebb, the behaviorial changes found by previous investigators cannot be attributed solely to the particular location of the neoplasm. No one would deny that widespread brain dysfunction probably occurs in patients with cerebral neoplasms. Changes in cerebral circulation, increased intracranial pressure, altered cerebral metabolism, and generalized electrical abnormalities are frequent sequelae to a brain tumor. Patients without space-occupying masses of the cerebrum, e. g., patients with epileptogenic foci on the EEG, may show no decrease on standardized intelligence scales after massive bilateral frontal lobectomy.[10] In fact, the patient may do better postoperatively. In rebuttal, Goldstein has claimed that these findings are inconclusive, since the special tests, which Goldstein feels are necessary to reveal the unique defects which characterize patients with frontal lobe lesions, were not employed.[7b]

In recent years, the investigators forming the Columbia-Greystone Associates [11] have used many special tests on patients with partial resections of the frontal lobes for psychogenic disorders. In these patients without cerebral neoplasms, they found no permanent postoperative change in associative memory, psychometric intelligence, or performance on sorting tests similar to those previously used by Halstead and Goldstein. Transient decreases in performance were found postoperatively.

7. (*a*) Gelb, A., and Goldstein, K.: Psychologische Analysen hirnpathologischer Fälle, in Ellis, W. D.: Source Book of Gestalt Psychology, New York, Harcourt, Brace and Company, Inc., 1938. (*b*) Goldstein, K.: The Mental Changes Due to Frontal Lobe Damage, J. Psychol. **17**:187, 1944. (*c*) Goldstein, K. and Scheerer, M.: Abstract and Concrete Behavior: An Experimental Study with Special Tests, Psychological Monographs, No. 53, pp. 1-151, No. 239, 1941.

8. Goldstein, K.: After-Effects of Brain Injuries in War, New York, Grune & Stratton, Inc., 1942; footnote 7*b*.

9. Hebb, D. O.: Man's Frontal Lobes: A Critical Review, Arch. Neurol. & Psychiat. **54**:10, 1945.

10. (*a*) Hebb, D. O.: Intelligence in Man After Large Removals of Cerebral Tissue: Report of Four Left Frontal Lobe Cases, J. Gen. Psychol. **21**:73, 1939. (*b*) Hebb, D. O., and Penfield, W.: Human Behavior After Extensive Bilateral Removal from the Frontal Lobes, Arch. Neurol. & Psychiat. **44**:421, 1940.

11. Columbia-Greystone Associates: Problems of the Human Brain: I. Selective Partial Ablation of the Frontal Cortex, edited by Fred A. Mettler, Vol. I, New York, Paul B. Hoeber, Inc., 1949.

but the changes were slight and disappeared within three months. The interpretation of these essentially negative results is complicated by the fact that the amount of cerebral tissue removed in these patients was relatively small. In addition, the behavior of these patients was markedly abnormal prior to surgery.

From the foregoing, it would seem that intellectual changes occur most frequently in patients with frontal lobe lesions and are particularly marked in patients with neoplasms. Such a deduction is more apparent than real. It is known that inflammatory, degenerative, and traumatic lesions can also produce severe mental changes. Goldstein, among others, found that shrapnel wounds of the frontal lobes produced the same sort of "loss of the abstract attitude" as did tumors.[8] Apparently, a space-occupying mass is not absolutely necessary to obtain gross intellectual defects. As for localization, it has been shown [12] that penetrating gunshot wounds of the parieto-temporo-occipital areas can result in the same degree of difficulty with special complex tasks (including figure-ground discrimination, sorting tests, and problem solving) as similar lesions of the frontal areas. Moreover, previous clinical observations on a large number of patients revealed that there was no specific area of the brain which when destroyed produced consistent mental changes. The intellectual changes noted in patients with tumors of the frontal,[13] temporal,[14] parieto-occipital,[15] or even subtentorial areas [16] were about the same in quality, although less frequent in the last instance. Evidently, etiology (a space-occupying mass), location (frontal lobe involvement), and special tests are not prerequisites for noting changes in intellectual function after cerebral damage.

In our previous studies we found that patients with cerebral gunshot wounds performed very well, as compared with control subjects with peripheral nerve injuries.[12] Evidence for defective performance could be obtained only on a group basis because there was large individual variability within both the brain-damaged and the control groups. Since the defects found were relatively small, as compared with the results reported in the literature, we suggested that patients with cerebral neoplasms might show greater defects than patients with shrapnel wounds of the brain. As Hebb [9] pointed out, however, cerebral tumors probably produce diffuse brain dysfunction in addition to the local effects resulting from the site of the lesion. In order to evaluate the effects of anteriorly or posteriorly situated neoplasms on intellectual ability, some sort of control over such widespread factors as altered cerebral metabolism, intracranial pressure, and electrical abnormalities appears essential.

In summarizing the literature, it seems likely that the most marked change in intellectual function is apt to occur in patients with cerebral neoplasms. Whether

12. (*a*) Battersby, W. S.; Teuber, H. L., and Bender, M. B.: Problem-Solving Behavior in Men with Frontal or Occipital Brain Injuries, J. Psychol. **35**:329, 1953. (*b*) Teuber, H. L.; Battersby, W. S., and Bender, M. B.: Performance of Complex Visual Tasks After Cerebral Lesions, J. Nerv. & Ment. Dis. **114**:413, 1951.

13. Strauss, I., and Keschner, M.: Mental Symptoms in Cases of Tumor of the Frontal Lobe, Arch. Neurol. & Psychiat. **33**:986, 1935.

14. Keschner, M.; Bender, M. B., and Strauss, I.: Mental Symptoms in Cases of Tumor of the Temporal Lobe, Arch. Neurol. & Psychiat. **35**:572, 1936.

15. Keschner, M.; Bender, M. B., and Strauss, I.: Mental Symptoms Associated with Brain Tumor, J. A. M. A. **110**:714, 1938.

16. Keschner, M.; Bender, M. B., and Strauss, I.: Mental Symptoms in Cases of Subtentorial Tumor, Arch. Neurol. & Psychiat. **37**:1, 1937.

or not the severest and most frequent defects occur in patients with neoplasms in the frontal lobes remains to be demonstrated. Apparently, new and special methods of testing are needed to evaluate further the intellectual ability of the brain-injured. In this respect, the type of tests initially introduced by Goldstein,[8] and used in our earlier study,[12b] seems to have heuristic value. Such tests should be combined with standardized tests to make the results comparable with the work of others.[10a]

The Objective.—In the present study, psychometric intelligence, figure-ground discrimination, and tests of "abstract" ability (sorting to criterion) were evaluated. Patients with space-occupying lesions of the frontal or posterior half of the brain

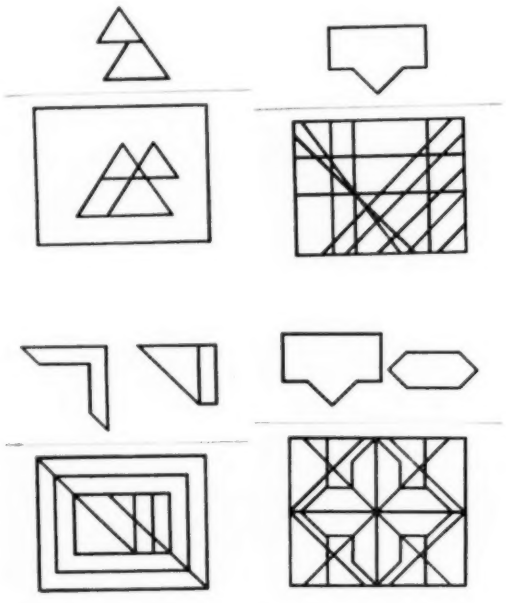


Fig. 1.—Specimens of figure-ground discrimination test.

were compared with patients with generalized increased intracranial pressure and electrical abnormalities, so that we might analyze what role the location of the lesions played in the production of the defects.

II. METHOD AND MATERIALS

A. Subjects.—A series of 64 patients were studied. Forty of these had lesions of the cerebral hemispheres (experimental group). All these patients were cooperative enough to be tested and had radiological (angiographic, pneumoencephalographic, or ventriculographic) and/or surgical evidence of space-occupying lesions in the cerebral hemispheres. In six of these patients the lesions were verified at autopsy. This group of 40 patients was divided into three classifications (*A*) patients with anterior, or pre-Rolandic (frontal), lesions; (*P*) patients with posterior or post-Rolandic (parieto-temporo-occipital), lesions, and (*I*) patients in whom the neoplasm lay in both pre- and post-Rolandic areas (intermediate lesions).

The remaining 24 patients served as a control group. These controls consisted of (1) patients with either generalized increased intracranial pressure, due to neoplasms in the posterior fossa, or idiopathic intracranial hypertension,[17] and (2) patients with spinal cord tumors. All patients were examined both before and after operation on all tests where possible.

B. Procedures.—Testing procedures used were similar to those in our earlier study on the effects of cerebral gunshot injuries [12b]:

1. A modified form of Gottschaldt's hidden figures [18] was used to test for figure-ground visual discrimination (Fig. 1). In this task the patient was asked to pick out a specified figure from a complex background by tracing it with a colored pencil. Some of these discriminations were relatively easy and others more difficult. There were 25 discriminations in all; the subject was allowed a maximum of two minutes for each one. Results were scored in terms of total number of errors and the total time required to complete the test.

2. A Weigl type of sorting test [19] was used to evaluate "abstract" thinking. In this procedure, the patient was required to sort a deck of 81 cards into three groups, each group being placed beneath one of three stimulus figures. Correctness of sorting was determined by one of

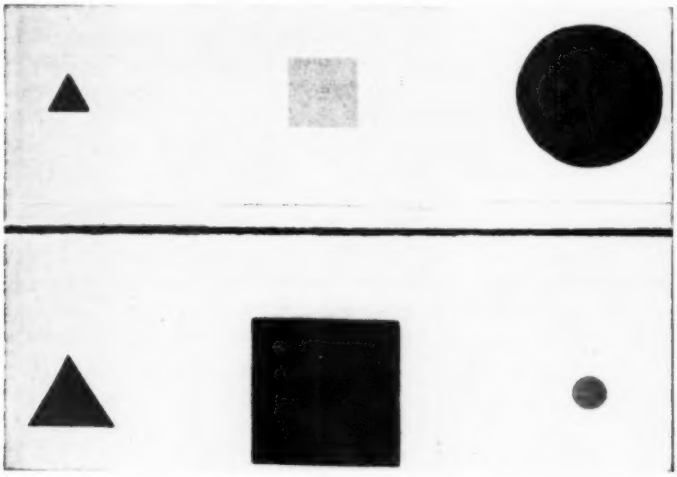


Fig. 2.—Specimen of sorting test.

three criteria: form, size, or brightness. In Figure 2, the three stimulus figures are shown at the top, and some cards that have already been sorted for form are shown beneath them. Subjects were not informed of the criteria to be used in sorting, but were simply told "right" or "wrong" after each card had been matched with one of the three stimulus cards by placing it at the bottom. The three criteria of sorting were alternated during testing in a predetermined random order, the subject being informed each time the criterion was changed. Results were scored in terms of the total number of errors made in sorting the 81 cards.

17. The etiology in these cases could not be ascertained. Clinical laboratory, roentgenological, and surgical studies disclosed increased intracranial pressure, but there was no evidence of a tumor or distortion or enlargement of the ventricular system.

18. Gottschaldt, K.: Über den Einfluss der Erfahrung auf die Wahrnehmung von Figuren I. Psychol. Forsch. **8**:261, 1926; Über den Einfluss der Erfahrung auf die Wahrnehmung von Figuren II, ibid. **12**:1, 1929.

19. Grant, A. D., and Berg, E. A.: A Behavioral Analysis of Degree of Reinforcement and Ease of Shifting to New Responses in a Weigl-Type Card-Sorting Problem, J. Exper. Psychol. **38**:404, 1948. Weigl, E.: On the Psychology of So-Called Processes of Abstraction, translated by Margaret J. Rioch, J. Abnorm. & Social Psychol. **36**:3, 1941.

3. Wechsler-Bellevue Form I was used to evaluate psychometric "intelligence" on both verbal and performance items. The methods of administration and scoring were standard. Results were expressed in terms of the raw scores in order to avoid statistical assumptions concerning standardization.

III. RESULTS

A. Quantitative Data.—The Table presents the results obtained on all tests both before and after operation. The number of subjects (N) is given, along with the group mean scores on each test. The differences between preoperative and postoperative test results are shown, the sign indicating the direction of change. Since the sorting test and figure-ground test were scored for errors, or time, a decrease in score indicates an improvement in ability and is given a positive value. The Wechsler-Bellevue tests, however, are scored for number correct. Since higher score values therefore indicate a greater ability of the subject, negative differences are shown on this test when the patient's score went down. Data for four groups of

Mean Preoperative and Postoperative Test Scores per Group

		Figure-Ground Discrimination			Sorting		Wechsler-Bellevue Form I		
								Raw Scores	
Subject Group	Operative	N	No. of Errors	Time, in Min.	N	No. of Errors	N	Verbal	Performance
Control	Preop.	23	6.6	17.7	22	19.8	22	57.5	78.7
(C)	Postop.	16	4.2	15.1	13	21.8	14	59.1	77.5
	Diff.	..	2.4	2.6	..	−2.0	..	1.6	−1.2
Anterior	Preop.	9	9.8	19.7	8	26.3	7	42.3	50.7
(A)	Postop.	12	11.4	24.6	11	27.7	11	39.3	47.1
	Diff.	..	−1.6	−4.9	..	−1.4	..	−3.0	−3.6
Posterior	Preop.	15	12.1	24.9	13	31.6	15	50.5	54.8
(P)	Postop.	9	9.4	24.9	8	25.9	8	49.3	63.1
	Diff.	..	2.7	0.0	..	5.7	..	−1.2	8.3
All cerebral	Preop.	31	10.7	23.0	27	29.3	28	48.2	56.1
neoplasms	Postop.	26	9.3	23.1	23	27.6	23	43.5	54.6
(A + P + I)	Diff.	..	1.4	−0.1	..	1.7	..	−4.7	−1.5

subjects are given: (C) control group, including patients with spinal cord or posterior fossa tumors, or with intracranial hypertension of unknown origin; (A) anterior group, including patients with pre-Rolandic (frontal) tumors; (P) posterior group, including patients with post-Rolandic (parieto-temporo-occipital) tumors; and (A + P + I) a combined group, including groups A, P, and I, the last being patients with lesions involving both the pre- and the post-Rolandic area (intermediate lesions).

1. Visual Figure-Ground Discrimination: Control subjects made less errors, and took less time, on this test than the anterior (A) or the posterior (P) group, or all brain tumor patients combined (A + P + I). Statistical analysis indicates that the differences between the controls and each of the brain-injured groups are significant [20] both preoperatively and postoperatively. There is no significant difference, however, between the anterior and the posterior group. Moreover, there is no significant difference between preoperative and postoperative scores for any of the experimental groups or for the controls.

20. All differences stated as significant had a chance occurrence of $P = 0.05$ or less.

2. Sorting Test: Mean error scores, per group, are given in the Table. On this test control subjects again made less errors than any of the other groups. A statistically significant difference in error scores can be found between the controls and each of the brain-injured groups both preoperatively and postoperatively. There is no significant difference, however, between the anterior and the posterior group. In addition, no significant differences can be found between preoperative and postoperative testing for either the experimental or the control subjects.

3. Wechsler-Bellevue Form I: Group mean raw scores for both verbal and performance scales are given in the Table. As in the other tests, a statistical analysis of these data shows a significant difference between the control group and each of the brain-injured groups on both verbal and performance scales. No significant difference can be demonstrated between the anterior and the posterior group; nor is there any significant difference between preoperative and postoperative data for either experimental or control groups.

B. Qualitative Observations.—The results shown above indicate that space-occupying lesions in the cerebral hemispheres produce a significant defect in the ability to discriminate figure from ground, to sort cards to "abstract" criteria, and to perform well on the Wechsler-Bellevue test. The degree of these particular defects appears to be much less than one would have predicted from the available literature.

On an individual basis, the defects noted above varied in severity within each group. It was only in the extreme case that the performance of the subject with cerebral damage appeared to differ qualitatively from that of the control. In the extreme cases the patients with cerebral hemispheric lesions became easily confused during testing, often became agitated, and expressed violent dislikes to the testing procedures. Frequently, they seemed to be responding only to specific aspects of the stimuli ("concreteness") and showed marked tendencies to perseverate in their responses. However, these qualitative changes in behavior appeared with equal frequency both in patients with anteriorly and in patients with posteriorly situated lesions. Occasionally some of these changes were noted in the control group.

The nature of some of the defects found on the experimental tests remains obscure, even in those patients with noticeable qualitative changes in behavior. There were several patients, for example, who matched all of the cards in the sorting test only for form, despite the examiner's repeated hints and statements that these matches were wrong. At the end of testing, however, these patients often correctly repeated verbally all three of the criteria of sorting, although they never had used all of them! Certainly, one cannot name this purely a defect in "abstract thinking." Instead, there seems to be a tendency for these patients to perseverate in the use of one preferred criterion, even though they are aware of alternate possibilities. Although there were rigidity and fluctuation in the performance of many subjects, control and experimental alike, these phenomena do not define the nature of these defects any further.

Other patients with extensive cerebral lesions performed exceptionally well on all tests. For example, there was one patient with a bilateral frontal lobe astrocytoma who made only 2 errors on the figure-ground discrimination (total time, 12.8 minutes) and 12 errors on sorting. Her full-scale Wechsler-Bellevue score was 105. This performance was much better than that of the average control

Postoperatively, her performance was slightly worse (a few more errors being made on each of the tests), but this frequently happened in the control group as well. Similar isolated examples of excellent performance on all tests were found in patients with parieto-occipital or temporo-occipital lesions.

In general, some patients with cerebral neoplasms showed marked qualitative alterations in behavior, while others with similar lesions did not. The test results in the majority of cases distributed themselves between these two extremes. In the control group with increased intracranial pressure there were occasional subjects whose qualitative behavior resembled that of the patient with a cerebral neoplasm. We have been unable, so far, to find any marked quantitative or qualitative differences between individual control patients and individual patients in the groups with cerebral lesions. All differences have been between groups of patients who overlapped in ability. Only a statistical analysis revealed the significance of these differences. These results are very similar to those obtained in our previous studies on the effects of cerebral gunshot wounds.[12]

IV. COMMENT

It is difficult to interpret the results of this study in terms of the literature dealing with intellectual deficits after cerebral damage. Traditionally, marked intellectual changes are usually interpreted as indicative of frontal lobe dysfunction and are often used clinically for purposes of localization.[18] In part, we can support this position, since some of our patients with frontal neoplasms showed qualitative alterations in intellectual processes. Identical alterations may occur, however, after lesions in the post-Rolandic areas, or even in patients without localized defects in the brain, such as those with intracranial hypertension. Conversely, other patients with pre- or post-Rolandic lesions may not show any intellectual changes either grossly or on special testing. Significant differences between patients with and without cerebral neoplasm can be found only on a group basis and must be evaluated statistically. It should be pointed out that these findings are not unique: Keschner, Bender, and Strauss,[21] in a clinical and statistical survey of over 500 cases of brain tumor, reported essentially the same conclusions some time ago.

One reason for not obtaining greater differences between individual patients in the control or experimental groups may be that the control group was highly selected. Our control subjects with posterior-fossa neoplasms complained of severe headache, showed neurological dysfunction, such as nystagmus, ataxia, and diplopia, and had marked increase in the intracranial pressure with "diffuse abnormality" in the electroencephalogram. It is precisely these features, however, that made them such an excellent control. Despite these symptoms and signs, their performance was superior to that of patients with cerebral lesions. One cannot explain the group defects demonstrated in the patients with supratentorial hemispheric lesions solely in terms of generalized intracranial pressure, or diffusely abnormal cerebral metabolism or electrical activity, since these factors were also present in control subjects with posterior fossa tumors. Moreover, the control subjects were located in the same wards, and were cared for by the same personnel, as the patients with cerebral neoplasms. In fact, they were even operated upon and treated by the same

21. Strauss and Keschner,[13] Keschner, Bender, and Strauss, footnotes 14, 15, and 16.

surgeons. In the case of those controls with idiopathic intracranial hypertension or posterior-fossa neoplasms, these operations consisted of subtemporal decompression or suboccipital craniectomy. One must conclude that the group defects found in the experimental subjects were largely due to the presence of a space-occupying mass in the cerebral hemispheres, and not to incidental factors, such as anxiety or reactive depression.

Our most striking and significant finding is that the incidence and severity of the group defects in our tests were approximately the same regardless of the location of the cerebral lesion. We have been unable to demonstrate any significant differences between patients with anterior and those with posterior lesions. There have been patients with frontal lobe lesions who did poorly on all tests; yet there have also been patients with lesions of similar size and location who performed well. Similarly, some patients with post-Rolandic lesions did fairly well on all tests, whereas others performed very poorly. In general, we have failed to find any significant quantitative or qualitative difference in the performance of these two subgroups. The patient group with post-Rolandic lesions did just as poorly on the three tests as that with pre-Rolandic lesions. Both these groups were inferior to the group with lesions below the tentorium, which served as part of our control.

The results of this investigation parallel those obtained in our previous experiments on patients with penetrating gunshot wounds [12b] and are similar to the clinical reports of Keschner, Bender, and Strauss [21] on the effects of brain tumors. In all these studies, patients with cerebral damage showed defects, but these defects could not be attributed to involvement of any particular cerebral area. It is an accepted fact that patients with large intracranial tumors show much more impairment of mental function than patients with penetrating gunshot wounds. We cannot be sure, however, that this comparison reflects a true difference in etiology, namely, between cerebral neoplasm and penetrating brain injury.

Up to this point, we have been preoccupied with the importance of such factors as the location and etiology of cerebral lesions, but there are many other factors which enter into a patient's performance. The age of the subject, his premorbid personality, and his medical and educational status require consideration. The younger the subject the less apt is he to have defects in perceptual performance.[22] Inasmuch as all our test performances are partly perceptual in nature, we must seriously consider age in the evaluation of our results. Patients with penetrating gunshot wounds in our previous studies consisted of veterans of World War II; they represented a group selected for military service on the basis of age and physical and psychiatric fitness. By contrast, patients with cerebral neoplasms characteristically fall within an older age group and may have a complicating history of systemic illnesses, including generalized arteriosclerosis, prior to admission. In addition, they represent patients selected for hospitalization.

It is impossible, therefore, to arrive at any clear-cut decision as to whether cerebral neoplasms are necessarily more functionally disturbing than penetrating gunshot wounds. The difference in age and medical status may be sufficient to explain the relative performance of patients with tumor or gunshot wounds of the cerebrum. One conclusion we can draw, however, is that the presence of a cerebral

22. Green, M. A., and Bender, M. B.: Cutaneous Perception in the Aged, A. M. A. Arch. Neurol. & Psychiat. **69**:577-581, 1953.

neoplasm in the frontal lobes is not a necessary condition for the so-called "intellectual" changes which have been previously reported in the literature. With neither gunshot wounds nor tumors of the cerebrum have we been able to demonstrate any deficit in complex visual tasks which was unique for patients with frontal-lobe damage. It would seem, therefore, either that so-called "intellectual" deficits specific for frontal lobe lesions do not exist, or that the tests necessary to demonstrate them have not been used in our studies.

At present, we are unable to explain to our own satisfaction the discrepancy between our results and the reports of some earlier workers. It is possible that the tests currently in use sample such a small segment of "intellectual" ability that slight differences between patients are not reflected in group statistics. This assumption implies that the behavior of the patient with a cerebral lesion must be evaluated in a situation where the intellectual function can be better analyzed both qualitatively [23] and quantitatively.[24] With such situational problems, the behavior of the brain-damaged person can be reduced to a descriptive level and attempts at measurement initiated. Using problem-solving situations of the Duncker-Maier [25] type, we have made some attempts to define further the problem in this way,[12a] but more work is needed before any definite conclusions can be drawn.

V. SUMMARY

Forty patients with neoplasms of the cerebral hemispheres were tested on a modification of Gottschaldt's figure-ground visual discrimination, a Weigl type of sorting test, and the Wechsler-Bellevue Form I. Twenty-four patients with either increased intracranial pressure of unknown origin or spinal cord tumors were used as control subjects. Results show that the group of patients with hemispheric lesions were significantly inferior in their performance on all tests to the control group. Individual patients, with or without cerebral damage, varied within wide limits on all the tests, precluding any simple interpretation of a qualitative change in performance after a brain lesion. No significant differences between patients with pre- or post-Rolandic lesions could be found. These results indicate that "intellectual" deficits may be produced by lesions in any portion of the cerebral hemispheres, and not chiefly by frontal lobe involvement, as some authorities are still claiming. More adequate testing methods are needed to aid in the definition and solution of the problem of intellectual functioning and brain injury.

23. Wertheimer, M.: Productive Thinking, New York, Harper & Brothers, 1945. Goldstein, K.: The Organism, New York, American Book Company, 1939.

24. Lashley, K.: Brain Mechanisms and Intelligence, Chicago, University of Chicago Press, 1929.

25. Duncker, K.: On Problem solving, Psychological Monographs, No. 270, 1945. Maier, N. R. F.: Reasoning in Humans: II. The Solution of a Problem and Its Appearance in Consciousness, J. Comp. Psychol. **12**:181, 1931; Reasoning in Humans: III. The Mechanism of Equivalent Stimuli and of Reasoning, J. Exper. Psychol. **35**:349, 1945.

REFLEXES IN INSULIN COMA

V. A. KRAL, M.D.
AND
C. C. SMITH, M.D.
MONTREAL, CANADA

THE DIFFICULTIES of ascertaining the depth of an insulin shock as currently used in the treatment of psychoses are well known. They are inherent in the hypoglycemic condition itself. After the insulin injection in a dosage high enough to produce hypoglycemic coma, the blood sugar level drops in the first two hours to from 20 to 30 mg. per 100 cc. No further drop occurs during the following hours, although the deepening coma and a number of neurological and vegetative signs indicate a continuous and progressive depression of brain activity. Himwich [1] demonstrated this to be a result of a decrease in the oxygen metabolism of the brain. Accordingly, different clinical pictures may be present with the same blood sugar level.

Clinicians have tried to find practical methods by which to assess the depth of an insulin shock, since with increasing experience the dangers connected with too deep a shock became known. Considerable attention has been devoted to the degree of impairment of consciousness present in the individual hypoglycemic condition. A survey of the literature, however, shows that complete agreement has not been reached about what should be called an "insulin coma." Some authors divide the comatose condition into "pre-coma" and "coma." In the former some reaction may be obtained on stimulation, whereas in the latter the patient does not respond even to strong stimulation. Kalinowsky and Hoch [2] stress the practical usefulness of such a differentiation.

Loss of consciousness, however, is only one, although perhaps the most impressive, sign of depression of brain function. Frostig [3] has pointed out that after loss of consciousness has occurred other objective signs are necessary to determine the depth of the underlying condition. Reflex changes, spontaneous neurological and vegetative phenomena, may thus be used for this evaluation.

Lups and Kramer [4] believe that reflex changes develop in a certain sequence and offer clear evidence of the depth of the insulin shock at any given moment. According

From the Verdun Protestant Hospital.

1. Himwich, H. E.: Brain Metabolism and Cerebral Disorders, Baltimore, Williams & Wilkins Company, 1951.

2. Kalinowsky, L. B., and Hoch, P. H.: Shock Treatments, and Other Somatic Treatments in Psychiatry, Psychosurgery, Ed. 2, New York, Grune & Stratton, Inc., 1952.

3. Frostig, J. P.: Clinical Observations in the Insulin Treatment of Schizophrenia: Preliminary Report, Am. J. Psychiat. **96**:1167-1190, 1940.

4. Lups, S., and Kramer, F.: Das Verhalten der Reflexe im Insulinkoma, Schweiz. Arch. Neurol. u. Psychiat. **45**:213-229, 1940.

to these authors, the abdominal reflexes tend to disappear in the precomatose state, whereas loss of the corneal reflex and a positive Babinski sign are characteristic of the deep coma. The reflexes are hyperactive during the coma but may disappear when it lasts for a longer period. Kalinowsky and Hoch made the following observations: The superficial reflexes, particularly the abdominal reflexes, disappear first; the deep reflexes follow, with individual variations. Babinski's sign is usually present in the beginning of the coma but may be elicited also in deep stupor. The other pyramidal signs in the lower extremities are often absent. In the upper extremities, the different pyramidal signs usually are present at the same time.

In general, most authors agree that loss of the corneal reflex is a reliable sign of a deep coma. There is some difference of opinion, however, as to whether the coma should be allowed to proceed after the corneal reflex has disappeared or be terminated immediately. Attempts have therefore been made to find reflexes which would indicate a sufficient depth of the insulin coma without relying on such a marginal sign as loss of the corneal reflex. Zimmermann [5] states that blowing on the eyelid normally causes a reflex contraction of the orbicularis oculi muscle. Loss of this reflex would be indicative of a sufficiently deep but not injurious coma. Kino [6] uses the nasopalpebral reflex for the same purpose.

The purpose of the present study was to investigate whether during insulin shock treatment reflex changes occur with such a regularity that they could be used for the clinical assessment of the depth of a given insulin shock.

MATERIAL AND METHOD

Nine physically healthy female schizophrenic patients in the age range of 22 to 53 years (mean age, 32.5 years) with normal neurological findings were closely investigated during 35 insulin shocks. Crystalline insulin in doses varying from 100 to 400 units (with an average of 250 units) was given to the fasting patient at 6:30 a. m. by the intramuscular route. At half-hour intervals until the termination of the hypoglycemic state (usually at 10:30 to 11 a. m.) the following conditions and signs were examined and noted: state of consciousness and general behavior; vegetative condition, spontaneous neurological phenomena (muscular twitching, tonic spasms, etc.), and a series of signs and reflexes (see below).

The ability of the patient to respond to questioning, commands, and verbal and physical stimuli was used as the criterion in ascertaining the state of consciousness. Particular attention was paid to perseveration, verbigeration, and echolalia. When the patient had lost contact with the environment, sensory stimuli were applied in increasing strength. Pinching of the axillary fold and of the interdigital web was found to be the strongest stimulus.

Subcoma was considered to be present when the patient did not respond to verbal stimuli but still would react to strong sensory stimuli. It was noted that during this subcomatose phase some patients showed an increased, that is, a generalized, reaction to stimulation. They would toss themselves around and display increased muscular twitching. It was only after the patient ceased to react to any stimulus, including pinching of the axilla, that we considered full coma to be present.

Neurological signs and reflexes investigated included (1) size and form of pupils; (2) reaction to light; (3) extrinsic eye movements; (4) corneal, nasopalpebral, and nasolabial reflexes; (5) abdominal reflexes; (6) deep reflexes in the upper and lower extremities, and (7) pyramidal signs in the upper and lower extremities.

5. Zimmermann, F. F.: Klinische und serologische Untersuchungen nach grossen Insulindosen, Monatsschr. Psychiat. u. Neurol. **100**:248-313, 1938.

6. Kino, F. F.: The Nasopalpebral Reflex: Its Application to Neuropsychiatry; Particularly to Insulin Shock Treatment, J. Ment. Sc. **95**:143-147, 1949.

RESULTS

Among the 35 hypoglycemic shocks investigated, full coma was achieved in 17 and subcoma in 18 instances.

In our observations vegetative changes accompanied all insulin shocks. Although with increasing severity of the hypoglycemic condition, as measured by the depth of impairment of consciousness, the vegetative changes tended to increase, the parallelism was not a strict one. There were variations as to both the kind and the degree of the vegetative signs.

Perspiration occurred in 29 of 35 insulin shocks; 6 shocks were "dry." Salivation of noticeable intensity was found in eight shocks—six of them were full comas and two subcomas. Changes in the pulse frequency were noted in 31 shocks. In 23 tachycardia was observed, the pulse rate in some being as high as 140 per minute. Bradycardia with pulse frequencies under 60 were noted in two shocks—one subcoma and one full coma. Markedly labored respiration occurred in four subcomas and one full coma. Deep cyanosis occurred in one deeply comatose patient. It would seem safe to assume on the basis of our observations that what is seen oftenest in insulin shocks of medium intensity is sympathetic stimulation. As Himwich has pointed out, however, medical examination per se may lead to sympathetic stimulation even in a subject who is in a state of parasympathetic predominance.

Regarding the spontaneous neurological phenomena during insulin shock, our observations tend to confirm Kalinowsky and Hoch's statement that great variations occur. No spontaneous signs of any kind were observable in 7 out of 35 shocks, that is, in 20%. Five of the seven were subcoma and two full-coma shocks. These patients went into subcoma or full coma quietly, without any sign of restlessness, muscular twitching, choreatic jerks, or tonic spasms.

General restlessness (throwing themselves about, tossing from side to side, grimacing, and moaning) was observed in 21 shocks. It occurred spontaneously but was increased by any approach to the patient, e. g., during the examination. Muscular twitching of myoclonic type and choreatic jerks were noted in 14 shocks, usually together with general restlessness. These were slightly more frequent in full-coma than in subcoma shocks (8:6) and usually occurred before the full coma developed.

Tonic muscular contractions of the decerebrate rigidity type were noted in 14 shocks—3 subcomas and 11 full comas. They varied from periodically occurring extensor spasms of the lower extremities to complete rigidity with extension of all extremities and opisthotonus. Although usually this decerebrate phase followed the phase of extrapyramidal hyperkinesis, in three cases the latter was not noticeable at all. In one case the tonic spasms were followed by complete loss of muscle tone.

With regard to the individual reflexes investigated, it should be pointed out that a remarkable variability was noted throughout the entire course of the shock. For statistical evaluation, however, only the reflex findings observed at the maximal depth of the shock were used.

The following observations could be made: Changes in the size of the pupils were found in 15 of the 35 shocks. Constriction was prevalent in full comas; dilatation, in subcomas. The light reflex was normal in 12 instances (10 subcomas and 2 full comas). Impairment of this reflex, ranging from sluggish to missing light reaction, was found in 23 shocks (8 subcomas and 15 full comas). This difference in light reflex between subcoma and full-coma shocks proved statistically significant.

It should be mentioned also that in the course of the individual shocks impairment of the light reflex was missing as long as consciousness was unimpaired.

Of particular interest were the findings concerning the extrinsic eye movements. Fixation of the eyeballs either in the midline or in lateral deviation was found in all 17 shocks leading to full coma. Nystagmus or floating eye movements, which were present before the state of full coma was reached, disappeared when this was attained. In the subcoma shocks, fixation of the eye movements was found in 9 out of 18 instances, nystagmus in 2, and floating eye movements in 1. No impairment of the extrinsic eye movements was seen in six subcomas.

These observations agree fairly closely with those of Brill and Binzley,[7] who found impairment of eye movements a good indicator of the depth of an insulin coma. According to these authors, there appears in every insulin coma nystagmus with a slow and fast component, followed by pendular nystagmus or conjugate deviation of the eyeballs and terminating eventually in complete loss of all spontaneous eye movements. Brill and Binzley, however, claim that they were able to elicit caloric nystagmus even at this stage, but only until the point when respiratory depression occurred.

We were next interested in investigating the relationship between the corneal and the nasopalpebral reflex during insulin shock. We included the nasolabial reflex in

TABLE 1.—*Trigeminofacial Reflexes in Insulin Shock*

	No. of Shocks	Corneal			Nasopalpebral			Nasolabial		
		Norm.	Dim.	Abs.	Norm.	Dim.	Abs.	Norm.	Dim.	Abs.
Subcoma	18	11	5	2	10	8	..	5	9	4
Full coma	17	4	7	6	4	6	7	4	2	11
Total	35	15	12	8	14	14	7	9	11	15

our study, as Ekbom, Jernelius, and Kugelberg [8] have shown that this latter reflex functions on a related anatomical basis as the nasopalpebral reflex. A comparison of our findings is presented in Table 1.

It would appear from this Table that each of these trigeminofacial reflexes may be found physiological, diminished, or absent in full coma. In the subcoma group the nasopalpebral reflex was not found absent, although the corneal reflex was missing in two and the nasolabial reflex in four subcoma shocks. These differences, however, were not statistically significant. In full coma the nasolabial reflex was missing more frequently than the other two reflexes; but, again, this difference was not statistically significant.

With regard to the abdominal (skin) reflexes, the following findings were made: The abdominal (skin) reflexes were normal in 1 instance (subcoma), diminished in 4 (3 subcomas and 1 full coma), and absent in 30 (14 subcomas and 16 full comas). It would appear, therefore, that absence of the abdominal (skin) reflexes is a sensitive, although not a specific, sign of full coma. They may be only diminished but still elicitable in full coma, and they may be completely absent in subcoma.

7. Brill, H., and Binzley, R. F.: Involuntary Eye Movements as a Criterion of Depth of Insulin Coma, Am. J. Psychiat. **96**:177-181, 1939.

8. Ekbom, K. E.; Jernelius, B., and Kugelberg, E.: Perioral Reflexes, Neurology **2**:103-111, 1952.

Regarding the deep reflexes in the upper extremities, the following observations were made on the triceps and radial reflexes: They were found unchanged in 14 instances. In 15 shocks increase of these reflexes was observed. In five of these the initial increase was followed by diminution of reflex activity, with abolition of the reflexes in two. In six instances the reflex activity in the upper extremities was diminished throughout the shock. Although most of these changes were found in full coma shocks, there was no strict parallelism between them and the depth of the coma. Even among the 17 full-coma shocks, in 4 there were physiological deep reflexes in the upper extremities. In four instances the reflexes on one side were more affected than the contralateral ones. No relation to the laterality of the patient was noted.

In the lower extremities, the knee jerks remained physiological throughout 10 shocks. They were found increased in 19 shocks, but in 5 of them the reflex activity later constantly decreased with the progression of the shock. In six instances decrease of the knee jerks was observed initially and throughout the shock with final abolition. The corresponding figures for the ankle jerks were as follows: physiological activity

TABLE 2.—*Neurological Signs in Insulin Shock**

Signs	Full Comas	Subcomas	Total
Abdominal (skin) reflexes diminished or absent	17	18	35
External eye movement fixation	17	17	34
Babinski's sign	17	9	26
Pupillary reaction changed	16	8	24
Pupillary size changed	16	8	24
Knee jerks changed	15	8	23
Ankle jerks changed	14	11	25
Corneal reflex diminished or absent	14	10	24
Nasopalpebral reflex diminished or absent	13	7	20
Nasolabial reflex diminished or absent	13	8	21
Mayer's reflex diminished or absent	13	13	26
Hoffmann's sign	10	10	20
	2	1	3

* Signs are listed according to their frequency in full coma.

in 11; increase in 10, and increase followed by diminution in 7. Constant diminution with final abolition of the ankle jerks occurred in seven instances. As in the upper extremities, the changes occurred more frequently in full coma than in subcoma, but this was not consistent. The changes of knee and ankle jerks were usually identical, and no gross lateralization could be observed.

The following pyramidal signs were investigated: in the upper extremities, Hoffmann's sign and Mayer's metacarpophalangeal reflex; in the lower extremities, Babinski, Oppenheim, Chaddock, and Rossolimo signs.

Hoffmann's sign was found positive in only three instances, namely, in two full comas and one subcoma, whereas unilateral or bilateral diminution or absence of Mayer's reflex was noted in 20 out of 35 shocks. It occurred in 10 full comas and in 10 subcomas.

Of the pyramidal signs in the lower extremities, Babinski's sign was found most frequently, whereas the others were usually absent. Babinski's sign was found in 24 out of 35 shocks. It was present in 16 out of 17 full comas and in 8 out of 16 subcomas. It can be considered, therefore, a fairly reliable sign of full coma, as stated by Lups and Kramer.

Table 2 brings a synopsis of the neurological signs which, in our observations, accompany the different stages of insulin shock. The signs are listed according to the frequency of their occurrence in full coma. It would appear from this Table that there are certain neurological signs which are present in every full insulin coma, namely, diminution or absence of the abdominal reflexes and fixation of the eyeballs. Neither of these signs, however, is confined solely to full insulin coma, as both can be found in subcomas as well. Therefore, the two signs cannot be considered specific for full insulin coma.

There are other neurological signs which appeared in nearly all full insulin comas. These included (1) a positive Babinski sign; (2) changes in size and reaction of the pupils; (3) changes in the deep reflexes in the lower and (less frequently) in the upper extremities, and, finally, (4) diminution or absence of the nasolabial, nasopalpebral, and corneal reflexes. It should be mentioned, however, that the trigeminofacial reflexes do not appear in the top of Table 2, but are listed in its lower half. In other words, in our observation the corneal reflex does not play the important role assigned to it by many authors, nor does the nasopalpebral reflex disappear always earlier than the corneal reflex. Lups and Kramer's statement that deep insulin coma is always characterized by loss of the corneal and abdominal reflexes and a positive Babinski sign cannot be confirmed on the basis of our findings.

COMMENT

No single neurological sign or group of signs was found to be specifically indicative of subcoma or full coma in insulin shock. The variability of the reflex changes found by previous investigators has been confirmed again by our observations. This would indicate that the clinician working with insulin shock treatment has to consider the clinical picture in its entirety and cannot rely on a single reflex or group of reflexes as reliable guides in the assessment of the depth of the hypoglycemic state.

The variability of the neurological picture can, however, be understood to a considerable degree if the metabolic changes occurring in the nervous system during insulin shock are taken into consideration, as well as the physiological mechanisms of the reflexes involved.

Several authors (von Angyal,[9] Frostig,[3] Ross and Malzberg,[10] and Himwich[1]) point out that the depression of brain function affects the different levels of integration in a certain order, descending from the cortex to the basal ganglia, to the midbrain, and, finally, to the medulla oblongata. When the last structure is impaired, the deepest level of coma is reached, which is therapeutically the most effective, but also the most dangerous, stage of the shock. Frostig has expressed the opinion that the vegetative phenomena also follow a certain pattern during insulin coma. At first there is vegetative equilibrium, which is followed by sympathetic preponderance. There is then a return to vegetative equilibrium. Finally, in the deepest coma the parasympathetic system predominates.

9. von Angyal, L.: Über die motorischen und tonischen Erscheinungen des Insulinshocks: Beiträge zur Physiologie und Pathologie des menschlichen Stirnhirns bei der Insulinbehandlung Schizophrener, Ztschr. ges. Neurol. u. Psychiat. **157**:35-80, 1937.

10. Ross, J. R., and Malzberg, B.: A Review of the Results of Pharmacological Shock Therapy and Metrazol Convulsive Therapy in New York State, Am. J. Psychiat. **96**:297-316, 1939.

This sequence of events is accompanied by changes in the electroencephalogram. The lapse into unconsciousness is characterized by the disappearance of 10 per second (alpha) waves and the appearance of slow delta waves. These may offer an objective means for the assessment of the depth of the coma, as pointed out by Hoagland, Cameron, and Rubin,[11] who devised a "delta index" for this purpose.

It seems understandable, therefore, that reflexes with a long reflex arc reaching up to the cortical level, such as, for instance, the abdominal (skin) reflexes and Mayer's metacarpophalangeal reflex, would be affected already in the first stages of the hypoglycemic shock. Our observations tend to substantiate this assumption. The abdominal reflexes were found diminished or absent in practically all shocks investigated, whether the patient went into subcoma or full coma. Mayer's reflex was found diminished or absent in 20 out of 35 shocks, 10 of which were subcomas. The fact that not all of the shocks showed a diminution of Mayer's reflex may be consistent with the theory advanced by von Angyal.[12] He differentiates a frontal and a parieto-occipital type of regression of cerebral function in hypoglycemic shocks. The diminution or absence of the metacarpophalangeal reflex may well correspond to the frontal type. Foerster[13] states that the reflex arc involves the frontal cortex.

Another group of reflexes which under physiological conditions are inhibited by higher cerebral structures become increased or elicitable when this inhibition is weakened or lost. Such a mechanism would account for the increase in the deep reflexes of the upper and lower extremities and the appearance of pyramidal signs observed in our material. Increase of the deep reflexes occurred at one time or the other during the shock in almost all of the full comas and in about one-half of the subcomas, and Babinski's sign was observed in about the same frequency distribution (16 full comas and 8 subcomas). The fact, however, that in some shocks, particularly in subcomas, neither increase of the reflexes nor Babinski's sign was found would indicate that either a certain intensity of the hypoglycemic condition is needed to suspend the physiological inhibition of these reflex mechanisms or that other factors come into play.

Diminution of the deep reflexes occurred in two forms: Either it followed a preceding increase in about one-half the cases, or decrease of these reflexes was the only change noted. Two possible explanations offer themselves for an understanding of this phenomenon. As the diminution of reflex activity usually occurred at a time when other clinical signs indicated depression of brain stem function, it might be assumed that the reflex diminution may be due to depression of the reticular formation in the brain stem, which exerts a facilitatory influence upon lower motor neurons, as described by Magoun.[14] Another explanation may be

11. Hoagland, H.; Cameron, D. E., and Rubin, M. A.: The Electroencephalogram of Schizophrenics During Insulin Treatments, Am. J. Psychiat. **94**:183-208, 1937.

12. von Angyal, L.: Über die verschiedenen Insulinshocktypen und ihre neuro-psychopathologische Bedeutung, Arch. Psychiat. **106**:662-668, 1937.

13. Foerster, O.: Symptomatologie der Erkrankungen des Rückenmarks und seiner Wurzeln, in Handbuch der Neurologie, Bumke, O., and Foerster, O.: Berlin, Springer-Verlag, 1936, Vol. 5.

14. Magoun, H. W.: An Ascending Reticular Activating System in the Brain Stem, A. M. A. Arch. Neurol. & Psychiat. **67**:145-154, 1952.

that the insulin shock may involve also the peripheral nervous system, as indicated by the observations of Stern, Dancey, and McNaughton.[15]

There is a third group of functions and reflexes, which are based on structures situated in the brain stem itself. To this group belong the extrinsic eye movements and the pupillary, corneal, and allied reflexes.

Changes in size and reaction of the pupils were found in nearly all the full comas and about half the subcomas. This finding is in keeping with the fact that impairment and loss of consciousness have been observed with lesions of the brain stem. Cairns [16] points out that these lesions may be located at different levels, from the diencephalon to the medulla oblongata. Thus, changes in the pupillary reflexes accompanying unconsciousness in the hypoglycemic condition would indicate that the depression of brain function has reached the midbrain level. A similar explanation would apply to the fixation of the eyeballs, which in our material was observed in all full comas and about half the subcomas. This sign, too, seems indicative of involvement of the lower portion of the brain stem, as the functional depression must have reached the ocular muscle nuclei or/and practically all their supranuclear connections.

Our observations regarding the corneal and nasopalpebral reflexes do not confirm the findings of Lups and Kramer that full comas are always characterized by loss of these reflexes. Absence of the corneal reflex was found in only 6 out of 17 full comas. In seven the reflex was only diminished, and in four it was found normal. If we take into consideration that consciousness may be lost at higher brain stem levels, that is, before the hypoglycemic depression has reached the pons, it becomes conceivable that there may be found loss of consciousness with normal, diminished, or absent corneal reflexes. Diminution or absence of the corneal reflex, on the other hand, would indicate that the hypoglycemic depression has reached the pons.

The same considerations apply to the nasopalpebral and the nasolabial reflexes. Kugelberg [17] and Ekbom, Jernelius, and Kugelberg have investigated these and other facial reflexes both clinically and electromyographically. They were able to demonstrate that these reflexes consist of two responses: (1) an early, well-synchronized discharge with a short latency period, which they consider as a stretch reflex of the muscles involved (orbicularis oculi and orbicularis oris, respectively), thus confirming in part Wartenberg's [18] view, and (2) a late, asynchronous discharge with a long latency period. The afferent pathways for both responses were found in the trigeminal nerve, as already assumed by Glattauer [19] on the basis of his clinical studies on the nasopalpebral reflex. Both these reflexes may therefore be considered as trigeminofacial reflexes with the internuncial part of the reflex arc in the pons.

15. Stern, K.; Dancey, T. E., and McNaughton, F. L.: Sensory Disturbances Following Insulin Treatment of Psychoses, J. Nerv. & Ment. Dis. **95**:183-191, 1942.

16. Cairns, H.: Disturbances of Consciousness with Lesions of the Brain-Stem and Diencephalon, Brain **75**:109-146, 1952.

17. Kugelberg, E.: Facial Reflexes, Brain **75**:385-396, 1952.

18. Wartenberg, R.: The Examination of Reflexes: A Simplification, Chicago, The Year Book Publishers, Inc., 1945.

19. Glattauer, A.: Zur Physiopathologie und Klinik des Nasenrücken-Lid-Reflexes, Schweiz. Arch. Neurol. u. Psychiat. **44**:243-255, 1939.

No essential difference may thus be expected during insulin shock between the nasopalpebral and nasolabial reflexes, on the one hand, and the corneal reflex, on the other; nor was it found in our observation. Table 1 shows that in full coma both these reflexes, as well as the corneal reflex, could be found to be physiological, diminished, or absent. It should be mentioned, however, that loss of any one of these reflexes, although not indicative of full insulin coma per se, should be taken as a sign of functional depression of the lower brain stem.

SUMMARY

A series of neurological signs and reflexes were closely investigated in 35 insulin shocks leading to subcoma or full coma.

No single sign or group of signs was found specifically indicative of subcoma or full coma. Two signs, however—diminution or absence of the abdominal (skin) reflexes and fixation of the eyeballs—were observed in all full-coma shocks.

No essential difference could be found between three trigeminofacial reflexes investigated. Loss of any one of these reflexes in the hypoglycemic condition should be taken as a sign of functional depression of the lower brain stem. Full coma, however, may be present with only diminished or with normal activity of these reflexes.

Some theoretical implications of these findings are discussed.

Dr. George E. Reed, Medical Superintendent, permitted the publication of this study.

ANEURYSM OF THE POSTERIOR COMMUNICATING ARTERY

Report of Five Additional Cases

LEO MADOW, M.D.
AND
BERNARD J. ALPERS, M.D.
PHILADELPHIA

ANEURYSM of the posterior communicating artery appears to be associated with a readily recognizable clinical syndrome. This has been established by a number of investigations. There still remain, however, problems regarding diagnosis which require clarification. These include the separation of aneurysms of the posterior communicating artery from those of the internal carotid artery, and better refinement of the clinical features associated with the syndrome. Reference has been made in a previous contribution [1] to the clinical features of posterior communicating artery aneurysm. To this are added the results of further studies.

REPORT OF CASES

CASE 1.—*History.*—D. Y., a 58-year-old Negro housewife, was admitted to the neurological service of the Jefferson Medical College Hospital on Sept. 10, 1947, with a complaint of inability to open the left eye. She had been well until 10 months before admission, when one morning she arose and, on going to the bathroom, had a sudden sharp pain and loss of vision in her left eye. Her husband noticed that her left eyelid drooped, and the patient observed that when she lifted the lid she could see out of the left eye. The pain lasted only a few moments, and during this time she noticed a soft, buzzing sound in the left ear that appeared intermittently, about 10 times a minute. A generalized headache persisted for two weeks and then subsided somewhat, but was intermittent until the time of admission to the hospital. The noise in the left ear, which the patient described as a swishing sound, continued until her admission. In April, 1947, the patient was found to have a positive Wassermann reaction of the blood. She was given weekly intravenous and intramuscular injections, after which the ptosis of the left eyelid was somewhat improved. The pain continued to recur and the left eyelid drooped, for both of which conditions she sought further help. She had had an operation for abdominal abscess in 1920 in which one ovary was removed. The systemic review and family history were not significant.

Physical Examination.—On admission, the blood pressure was 130/80, the pulse rate 90, the respiration rate 20, and the temperature 98 F. There was a presystolic mitral murmur, which was transmitted to the axilla, but otherwise the general physical condition was normal.

Neurological Examination.—Visual acuity was 20/100 in the left eye and 20/70 in the right eye. The visual fields were normal. The fundi were well defined and of good color and showed moderate arteriosclerosis. The left pupil was larger than the right and was fixed to light and in accommodation. There was complete external ophthalmoplegia with sparing of the left external rectus. The left eye deviated externally, and there was ptosis of the left eyelid. The biceps, triceps, radial, and patellar reflexes were overactive and the Achilles reflexes decreased. The remainder of the neurological examination revealed no abnormality.

From the Department of Neurology, Jefferson Medical College of Philadelphia.

1. Alpers, B. J., and Schlezinger, N. S.: Aneurysms of Posterior Communicating Artery, Arch. Ophth. **42**: 353, 1949.

Laboratory Data.—The urine was normal. Blood studies revealed 68% hemoglobin, 3,500,000 red cells, and 5,000 white cells. The Wassermann and Kahn reactions of the blood were strongly positive. The spinal fluid was under an initial pressure of 160 mm., and was clear and colorless, with 2 cells per cubic millimeter, 28 mg. per 100 cc. of protein, and a doubtfully positive Wassermann reaction. The electrocardiogram showed a first-degree heart block. Roentgenograms of the skull were normal, and x-ray studies of the chest revealed cardiac enlargement. On fluoroscopic study of the chest an aneurysm of the descending thoracic aorta was seen. A cerebral arteriogram of the left internal carotid artery (Fig. 1) revealed an aneurysm of the posterior communicating artery measuring slightly less than 1 cm. in diameter seen just posterior to the cephalic extremity of the internal carotid artery, where it joined the circle of Willis.

Summary.—A 58-year-old Negro housewife was admitted with a 10-month history beginning with sudden sharp pain and loss of vision in her left eye and drooping

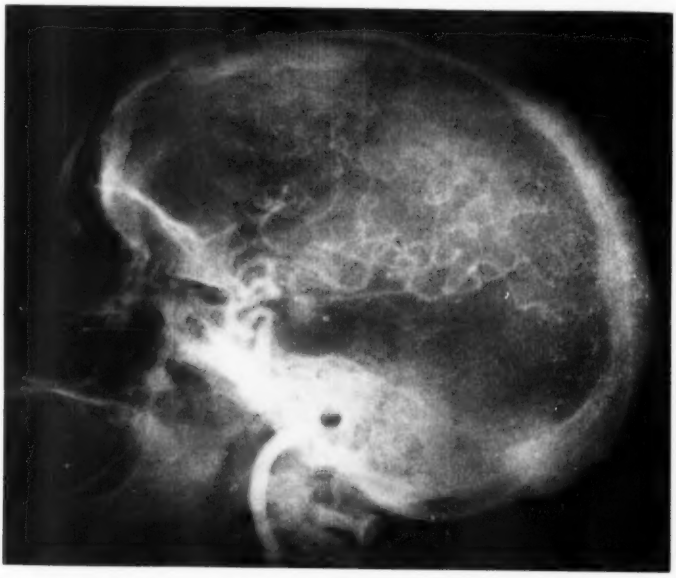


Fig. 1. (Case 1).—Arteriogram of left internal carotid artery, revealing aneurysm of posterior communicating artery.

of the left eyelid. Examination revealed the ptosis of the left eyelid and complete external ophthalmoplegia, with sparing of the left external rectus muscle. The left pupil was larger than the right and was fixed to light and in accommodation. This patient had a typical picture of aneurysm of the left posterior communicating artery, a diagnosis which was confirmed by arteriography. She was found also to have an aortic aneurysm. Operation was not carried out for this reason.

Case 2.—*History.*—E. W., a 53-year-old white housewife, was admitted to the neurological service of the Jefferson Medical College Hospital on Dec. 20, 1950, with the complaint of drooping of the left eyelid and double vision for approximately one month. She stated that one month before her admission to the hospital she had struck the left side of her head on entering an automobile but was not knocked unconscious. Two days later she awoke in the morning with dull pain over the left eye and pain on moving the eyeball. This persisted until her admission to the hospital. Some days later she noticed drooping of the left eyelid and

diplopia, and 10 days after this, excruciating pain developed in the top of her head and she vomited several times. After this a stiff neck and severe occipital headache developed. Five days later she was admitted to the Wills Eye Hospital, where examination revealed partial weakness of the left oculomotor nerve, involving chiefly the levator palpebrae and the superior rectus. The left pupil was larger than the right but reacted to light and in accommodation. The patient was found to have hypertensive cardiovascular disease. She was transferred to the Jefferson Medical College Hospital for further examination and treatment. The past history revealed that she had been treated for hypertension. The systemic review and family history were not contributory.

Neurological Examination.—Examination revealed nuchal rigidity, a positive Brudzinski sign, and a questionably positive Kernig sign. There were complete left oculomotor nerve paralysis and weakness of the left trochlear and abducens nerves. There was bilateral papilledema. The left pupil was larger than the right but reacted to light and in accommodation. The remainder of the neurological examination revealed nothing abnormal. The blood pressure was 150/110.

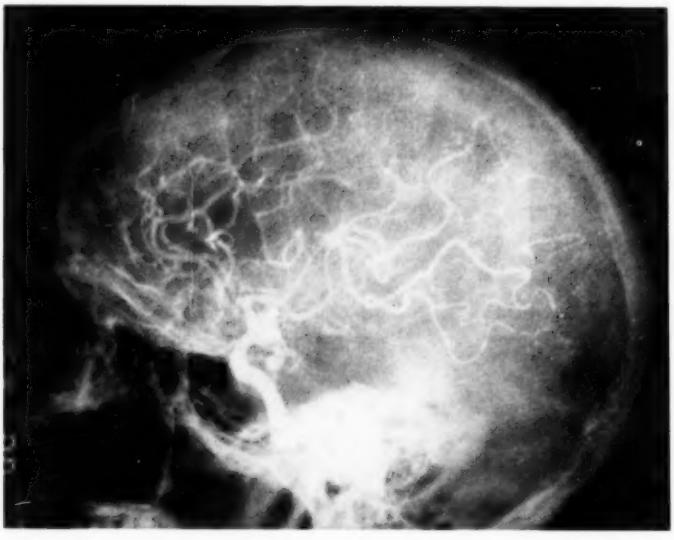


Fig. 2 (Case 2).—Left internal carotid arteriogram, showing aneurysm of left posterior communicating artery.

Laboratory Data.—The urine was normal. Routine blood studies gave normal findings. The Wassermann and Kahn reactions of the blood were negative. An electrocardiogram revealed occasional premature ventricular contractions and low voltage T-waves. Lumbar puncture showed an initial pressure of 230 mm. with xanthochromic fluid. Microscopic examination revealed many red blood cells. The Wassermann reaction of the spinal fluid was negative. A left internal carotid arteriogram (Fig. 2) revealed an aneurysm of the left posterior communicating artery.

Course.—Right hemiparesis and aphasia developed subsequent to the arteriogram, and postarteriographic convalescence was stormy. Severe mental aberrations developed. The hemiparesis persisted, but there was marked improvement in her mental state and in her expressive aphasia. On discharge she had complete ptosis of the left eyelid and left external squint, right facial paralysis, and right hemiparesis.

Summary.—The patient, a 53-year-old housewife, had a one-month history of drooping of the left eyelid and diplopia, following a blow to the left side of her head.

There then developed dull pain over the left eye, worse on movement of the eye. This progressed to severe occipital headache and nuchal rigidity. Examination revealed complete left oculomotor nerve paralysis and weakness of the left trochlear and abducens nerves. The left pupil was larger than the right but reacted to light and in accommodation. An arteriogram revealed an aneurysm of the left posterior communicating artery.

CASE 3.—*History.*—W. P., a 58-year-old white salesman, was admitted to the Pennsylvania Hospital on June 27, 1940, with the complaint of convulsive seizures for 2½ weeks. Eighteen days before he had had a convulsive seizure, after which he was paralyzed on the right side of the body for a few hours. This cleared, and he was well for five days, when he again had temporary loss of function of this side together with loss of speech. Again, there was little residual paralysis, but 10 days later he had a much severer seizure, this time involving the left side of the body. Recovery from this was much less complete, although he could voluntarily execute a few movements. At the time of admission he moved both arms and legs and tried to roll from side to side but did not open his eyes or attempt to speak.

General Physical Examination.—Examination revealed a slender, emaciated, semicomatose man, who occasionally moved his right arm to his face but rarely made movements with his left arm. The blood pressure was 184/96, and the pulse rate was 96 a minute. The general examination was otherwise normal.

Neurological Examination.—The right pupil was enlarged and the left pupil was small, neither reacting to light. The lids could be lifted without resistance, but ocular movements could not be tested because of the comatose state. The biceps and triceps reflexes were diminished bilaterally. The patellar reflexes were also diminished, but the Achilles response was active, being stronger on the left than on the right. The remainder of the neurological examination was unsatisfactory.

Laboratory Data.—Urinalysis revealed a slight trace of albumin. Blood studies showed 12.5 gm. hemoglobin per 100 cc.; 4,350,000 red cells, and 15,600 white cells. The Wassermann reaction of the blood was negative. The blood urea was 17 mg., and the serum protein 5.7 mg., per 100 cc., and the hematocrit reading was 20%. The blood culture was sterile. The spinal fluid contained 150 cells per cubic millimeter and the protein content was 20 mg. per 100 cc. The x-ray of the skull was normal.

Course and Necropsy.—The patient had a progressively downhill course and died two months after admission. Necropsy revealed a swollen brain with an old hemorrhage over the medial surface of the right temporal lobe and some hemorrhagic staining over the orbital surfaces of the frontal lobes. The oculomotor nerve on the right was enmeshed in a hemorrhagic mass, which was a ruptured aneurysm of the right posterior communicating artery. There was, in addition, an old area of hemorrhage into the right temporal lobe, particularly the hippocampal region. Fresh blood was seen in the entire ventricular system.

Summary.—A 58-year-old salesman had a 2½-week history of illness, beginning with a convulsive seizure, followed by transient paralysis of the right side. He had one recurrence of this and then another convulsion, this time involving the left side of the body. On admission to the hospital, he was semicomatose, and examination revealed an enlarged right pupil and a small left pupil, neither reacting to light. The course was downhill, and necropsy revealed a ruptured aneurysm of the right posterior communicating artery, as well as an old area of hemorrhage in the right temporal lobe.

CASE 4.—*History.*—A. T., a 33-year-old white housewife, was admitted to the Jefferson Medical College Hospital, to the service of Dr. Rudolph Jaeger, on Jan. 3, 1948, because of severe generalized headaches of two weeks' duration. She had had mild generalized headaches sporadically for years but was otherwise well until she became pregnant, in April, 1947, when she had mild nausea and vomiting. Eight months later she had dull head pains over the right eye and was told by a physician that she had neuralgia. This persisted for four days, when she

was awakened from sleep by a severe generalized headache, which radiated down both sides of the neck. Four days later she began to vomit and fell to her knees because of "an explosion of terrific generalized head pain." The next day she noted that the right eyelid drooped slightly and felt heavy. In view of the distressing symptoms, the small size of the pelvis, and a breech presentation, a Caesarean section was done. A dull generalized headache persisted, and the ptosis became more marked. She also noted that if she lifted the eyelid she saw double. She had a recurrence of the severe head pain and was admitted to the hospital.

The past medical history revealed that she had had her tonsils removed at the age of 21 because of "rheumatic pains." When she was 16, she fell and struck the right side of her head against a wooden step and was unconscious for a short time. She was told she had a slight concussion and was kept in bed for two weeks. She had had a normal pregnancy eight years previously.

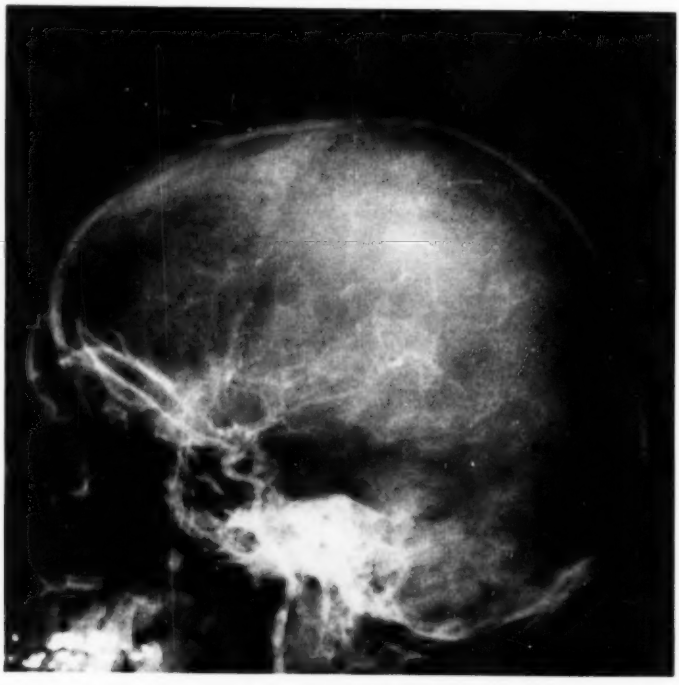


Fig. 3. (Case 4.)—Right internal carotid arteriogram reported as suggestive of aneurysm of the posterior communicating artery. Craniotomy confirmed this diagnosis.

General Physical Examination.—This was normal except for a recent abdominal incision. The blood pressure was 110/65.

Neurological Examination.—The right pupil was dilated and did not react to light or in accommodation. The right eyelid was completely ptosed, and there were paralysis of upward and downward gaze of the right eye and partial paralysis of inward gaze. There was some nuchal rigidity, but the remainder of the neurological examination revealed no abnormality.

Laboratory Data.—Urinalysis showed many pus cells and a slight amount of albumin. The hemoglobin was 84%, with 4,400,000 red blood cells and 7,900 white blood cells. The spinal fluid was reported to have been bloody at the time of the Caesarean section. Ventricular fluid was removed at operation and was clear, with a protein content of 16 mg. per 100 cc. X-rays of the chest and skull were normal. The history was suggestive of an aneurysm, either of the

internal carotid or of the posterior communicating artery on the right; and an arteriogram was done (Fig. 3), which was reported as suggestive of an aneurysm of the posterior communicating artery.

Operation.—A craniotomy was performed, and an aneurysm of the posterior communicating artery was found and isolated by silver clips. Recovery was uneventful.

Summary.—A 33-year-old housewife, with a long history of sporadic headaches, had severe generalized headache, more marked on the right, in the eighth month of her pregnancy. She then observed a slight drooping of the right eyelid, which became more pronounced after a Caesarean section. If she lifted the eyelid, she saw double. Examination revealed complete ptosis of the right eyelid with paralysis of upward and downward gaze and partial paralysis of inward gaze. The right pupil was dilated and did not react to light or in accommodation. An arteriogram was suggestive of an aneurysm of the posterior communicating artery. This was found at operation and isolated by silver clips. She made an uneventful recovery.

CASE 5.—*History.*—M. M., a 44-year-old Negro housewife, was admitted to the neurological service of the Jefferson Medical College Hospital on Nov. 7, 1945, with a complaint of drooping of the right lid for two weeks before admission. Early in September the patient had gone to bed because of menstrual cramps, and on the third day of her period she suddenly experienced severe pain in the right side of her head and the right cheek, radiating down into the neck. She went to her family physician, who treated her for neuralgia, with little relief. About 10 days later she noted double vision, which was followed four days later by ptosis of the right eyelid. This became worse, until on admission to the hospital the ptosis was complete. The pain was described as beginning in the right frontal region and spreading over the vertex "like a hammer hitting." She also had a severe pain over the right cheek and a burning sensation on the right side of the nose and maxilla. The headaches persisted, occurring two to four times a week, mostly at night, being aggravated by lying on the right side and relieved by sitting up or lying on the left side. The past history revealed that the patient had had some difficulty with her eyes when she was 3 years old and had had fainting spells at the time of menstruation. The systemic review and family history were not significant. The physical examination was normal.

Neurological Examination.—The right pupil was larger than the left, with loss of reaction to light and in accommodation. There was complete ptosis of the right lid with loss of movement of the right eye upward, inward, or downward. The remainder of the neurological examination revealed nothing abnormal.

Laboratory Data.—The hemogram revealed 55% hemoglobin, 3,500,000 red cells, and 9,500 white cells. The Wassermann and Kahn reactions of the blood were negative. Spinal fluid examination revealed an initial pressure of 170 mm. of water. The spinal fluid was clear, with 1 cell per cubic millimeter. The Wassermann reaction was negative, and the protein was 25 mg. per 100 cc. Visual fields were normal. Routine films of the skull were normal. Films of the sinuses showed some clouding of the left antrum, with a smooth, rounded shadow on its lateral surface, probably representing a mucocele on this side.

Course.—The patient refused operation, and, although a presumptive diagnosis of aneurysm of the posterior communicating artery was made, no operation or arteriographic study was performed. After her discharge she was observed in the neurological clinic and remained in relatively good condition until five weeks before readmission, when she experienced severe frontal headaches and pain over her right eye. This persisted until three days before admission, when she complained of severe pain over her right eyeball and a throbbing frontal headache. She also had pain in the back of her neck, with some stiffness. The pain became progressively worse, and she returned to the Jefferson Hospital on March 19, 1948, two years and four months after the first admission. At this time she was found to have nuchal rigidity, a positive Kernig sign, and complete right oculomotor paralysis. There were also paralysis of the right trochlear nerve and impaired sensation of the ophthalmic branch of the trigeminal nerve. A lumbar puncture revealed a grossly bloody spinal fluid. The pressure was 190 mm. and the protein

content 124 mg. per 100 cc. An arteriogram was obtained, and an aneurysm of the right posterior communicating artery was found. The right common carotid artery was ligated in an effort to control the subarachnoid hemorrhage, and at discharge she showed complete external and internal ophthalmoplegia on the right with sparing of the right sixth nerve. The headache was completely relieved. It was recommended that she have a ligation of the aneurysm, but this she refused.

Summary.—A 44-year-old housewife, with two admissions to the hospital over a 2½-year period, first complained of drooping of the right eyelid, severe pain in the right side of her head, and double vision. Examination revealed a dilated right pupil with loss of reaction to light and in accommodation. There was complete right ophthalmoplegia with sparing of lateral gaze, and the eyelid was completely ptosed. A presumptive diagnosis of aneurysm of the posterior communicating artery was made, but she refused operation and left the hospital. She returned two years and four months later because of return of the severe pain on the right side, when she had nuchal rigidity, as well as complete oculomotor and trochlear paralysis and impaired sensation over the ophthalmic branch of the trigeminal nerve. An arteriogram revealed an aneurysm of the right posterior communicating artery, and the right common carotid artery was ligated because of the subarachnoid hemorrhage. She refused to allow an operation for ligation of the aneurysm.

COMMENT

Incidence.—Although aneurysms involving the posterior communicating artery are not as frequently encountered as aneurysms in other parts of the circle of Willis, they occur with sufficient frequency to require careful differentiation from aneurysms involving adjacent vessels, particularly the internal carotid artery. In a previous communication,[1] it was pointed out by verified examples that the diagnosis of aneurysm of the posterior communicating artery could be established clinically. The incidence of such aneurysms has been found by various authors to be 1.4%,[2] 3.7%,[3] 4.9%,[4] 6.4%,[5] and 8.1%.[6] On the other hand, Dandy[7] reported no examples in his series of aneurysms. Though there is reason to believe, as Dandy maintained, that some of the posterior communicating artery aneurysms are in reality aneurysms of the internal carotid artery, there is good evidence that independent aneurysms of this vessel occur, although it may not be possible to indicate their incidence accurately.

The reason for the low incidence of aneurysms involving the posterior communicating artery may be found in the relative frequency with which this artery is absent or anomalous in normal circles of Willis. Stopford[8] found that absence of this artery was the most frequent cause of lack of completion of the circle of Willis. Among 100 unselected circles of Willis,[9] 4 had absence of posterior communicating arteries, and 12 had thin, string-like vessels, occurring bilaterally in 9.

2. Poppen, J. L.: Specific Treatment of Intracranial Aneurysms, J. Neurosurg. **8**:75, 1951.

3. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. **42**:298, 1939.

4. Epron, G.: Des aneurysmes intracraniens, Thesis, No. 82, Paris, 1890.

5. Hamby, W. B.: Intracranial Aneurysms, Springfield, Ill., Charles C Thomas, Publisher, 1952. Gull, W.: Aneurysms of the Cerebral Vessels, Guy's Hosp. Rep. **5**:281, 1859.

6. Lebert, H.: Über die Aneurysmen der Hirnarterien, Klin. Wchnschr. **3**:209, 1866.

7. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Co., Inc., 1944.

8. Stopford, J. S. B.: Arteries of Pons and Medulla Oblongata, J. Anat. & Physiol. **1**:131, 1916.

9. Unpublished data.

Clinical Features.—Aneurysm of the posterior communicating artery is associated with a history of unilateral headache, often eye pain, and either partial or complete paralysis of the oculomotor nerve. Though this syndrome is distinctive, it is not pathognomonic, since precisely the same group of symptoms may develop with aneurysm of the internal carotid artery. In the case of posterior communicating artery aneurysm, however, the involvement of other cranial nerves fails to develop unless there has been rupture of the aneurysm with subsequent subarachnoid hemorrhage. The vessel itself is small; the aneurysms arising from it rarely attain large size, and the parent vessel itself is in close relationship only to the oculomotor nerve. Although the trochlear nerve runs lateral to the oculomotor nerve, it is usually too far lateral to be compressed by the characteristically small aneurysm of the posterior communicating artery. The same is true of the abducens nerve, which is lateral and inferior. The ophthalmic branch of the trigeminal nerve is somewhat closer but is more anterior and is more likely to be affected by aneurysms of the internal carotid artery. Jefferson [10] indicated this with reference to the optic tract when he stated that the vessel most favorably situated to cause a lesion of the optic tract is the posterior communicating, but aneurysms of this artery are generally small and probably rupture before they have indented it enough to give rise to recognizable visual disturbances. Aneurysms of the internal carotid artery, on the other hand, often attain large size and not infrequently involve other cranial nerves without rupture of the aneurysm. The similarity of the clinical features of posterior communicating and some internal carotid artery aneurysms led Dandy to assert that, though most of the aneurysms lie on the posterior communicating artery, the sac actually enters the carotid artery. While this is probably true of most cases of a lesion regarded as aneurysm of the posterior communicating artery, there is also no doubt that aneurysms may involve this vessel without implication of the internal carotid artery. When only the oculomotor nerve is involved in a suspected case of aneurysm, it is impossible to distinguish clinically between an aneurysm of the posterior communicating artery and one involving the posterior wall of the internal carotid, as well as the posterior communicating, artery. It is possible to separate the two, however, by means of an arteriogram, which will often, but not always, indicate the source of origin of the aneurysm. In those instances, however, in which the aneurysm involves other cranial nerves beyond the oculomotor nerve, the probabilities are very much against aneurysm involving the posterior communicating artery and in favor of aneurysm of the internal carotid artery.

Beadles [11] pointed this out when he noted that the most constant signs of posterior communicating artery aneurysm are those produced by compression of the third cranial nerve. In aneurysms of the intracranial portion of the internal carotid artery, he stated, the nerve symptoms are associated principally with compression of the optic nerve, but the third nerve and others are sometimes involved. The third nerve, he added, may be compressed by rather small aneurysms of the internal carotid artery when their growth is in a backward direction, so as to occupy a position of the posterior communicating artery. When the latter condition occurs, these two aneurysms are indistinguishable clinically.

10. Jefferson, G.: Compression of the Chiasm, Optic Nerves and Optic Tracts by Intracranial Aneurysms, Brain **60**:444, 1937.

11. Beadles, C. F.: Aneurysms of Larger Cerebral Arteries, Brain **30**:285, 1907.

The exact incidence of isolated oculomotor nerve compression by aneurysms of the internal carotid artery cannot be determined. In Dandy's series of 18 patients with internal carotid aneurysms, 8 (Cases 7, 8, 10, 11, 12, 16, 17, and 18) had as their first symptoms headache and some oculomotor involvement. However, five of these (Cases 8, 11, 16, 17, and 18) either had or later manifested impaired vision on the side of the aneurysm. Of the three without visual disturbance, one (Case 7) had nystagmus and dizziness. He had a sacculated aneurysm of the right internal carotid trunk below the posterior communicating artery, which was clipped, and his symptoms cleared. Another patient (Case 10) had a small pea-sized aneurysm on the posterior wall of the internal carotid artery, reaching the third nerve. The third (Case 12) had a hazelnut-sized, round aneurysm filling the region of the third cranial nerve. Clips were applied above and below the neck of the aneurysm, and symptoms cleared.

Thus, Dandy's three internal carotid aneurysms which clinically resembled aneurysms of the posterior communicating artery were small and extended posteriorly, compressing the third nerve. Two of the three responded to surgery. The third ruptured at operation, and the internal carotid artery had to be coagulated, leading to its rupture one month later. When the aneurysms become larger, other cranial nerves are involved, so that it is only the small aneurysms of the internal carotid artery which resemble aneurysms of the posterior communicating artery clinically.

Of our patients, all five had some evidence of oculomotor nerve involvement. Of the four who could be examined completely, all had ptosis of the affected eyelid. This was one of the early signs. All five had pupillary dilatation, and in four of the five the pupil failed to react to light. Of the four patients who could be examined, all had paralysis of the extraocular muscles supplied by the oculomotor nerve.

Ptosis of the eyelid in posterior communicating artery aneurysm, which is one of the earliest signs, is, of course, the result of interruption of the nerve fibers of the oculomotor nerve to the levator palpebrae. Whitnall [12] stated that the fibers to the levator palpebrae run on the surface of the oculomotor nerve and are therefore affected by pressure or compression of the nerve, with resulting ptosis. The failure of the pupil to react to light is also an early sign, and Walsh [13] stated that the pupillary fibers are also peripherally situated and are therefore similarly susceptible. He substantiated Whitnall's claim, stating that one of the early evidences of involvement of the oculomotor nerve at the base is the onset of ptosis, since that portion of the nerve which serves the levator muscle is particularly exposed. Walsh stated further:

> In our experience, unilateral paralysis of the 3rd nerve in an individual who has complained of sudden severe pain in and about the eye always suggests aneurysm of congenital type, often arising from the internal carotid or posterior communicating artery.

In addition to the oculomotor nerve paralysis, two patients (Cases 2 and 5) had weakness of the superior oblique, and one of these (Case 2) had lateral rectus paralysis as well. Both these patients had leakage of their aneurysms as shown by signs of meningeal irritation and blood in the spinal fluid. The fifth patient was hospitalized twice over a 2½-year period and on the first admission showed only oculomotor nerve paralysis. When her aneurysm ruptured, 2½ years later, she had not

12. Whitnall, S. E.: Anatomy of Human Orbit and Accessory Organs of Vision, Ed. 2, London, Oxford University Press, 1932.

13. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947.

only the oculomotor involvement but trochlear nerve paralysis and impaired sensation over the ophthalmic branch of the trigeminal nerve. This would appear to substantiate the impression that unruptured aneurysm of the posterior communicating artery involves only the oculomotor nerve and that other cranial nerves are affected only when it leaks.

Angiography.—Although most authors [14] state that arteriography is the method of choice in the diagnosis of aneurysms, very few discuss the reliability of this technique either in revealing an aneurysm when present or in delineating its origin. List and Hodges [14a] stated that no other diagnostic method surpasses angiography in accuracy not only in the location and size of an aneurysm but also in revealing multiple aneurysms. On the other hand, they indicated that angiography has its limitations. For instance, the aneurysmal sac, as seen in the arteriogram, may be smaller than the aneurysms found at operation or autopsy if it is partially obliterated by clot.

If the aneurysm or its neck is very small, the pouch may not accept any of the contrast medium. In other cases the sac may appear larger if rupture has occurred and the hemorrhagic mass has been walled off by the neighboring tissue. Lima [14c] stated that it is sometimes easier to determine the point of origin of an aneurysm by examining the angiographic image than by dissecting it in the cadaver. Hamby,[15] in a series of 22 cases of aneurysm, found 4 in which the angiogram did not indicate the aneurysm found at autopsy. One of these was a case of aneurysm of the posterior communicating artery; in the other three the aneurysm was of the anterior communicating artery. In his series of patients whom he studied for subarachnoid hemorrhage, he found that 41% showed aneurysms by angiography, whereas 93.6% were observed to have aneurysms at autopsy. He stated that even complete angiography does not insure that all aneurysms will be visualized. This is understandable on the basis of the dynamics of fluid flow in tortuous tubes, the size of some of the lesions, and on the likelihood of partial thrombosis in some of the aneurysms. Of the present group of five patients, four had positive arteriograms. Of these four, one was operated on (Case 4) and the aneurysm was found. In Case 3 no arteriogram was performed, but the aneurysm was found at autopsy. In this case the history was unique in that the symptoms started with convulsive seizures and progressed to hemiplegia. The patient was seen in a semicomatose state, and owing to limitation of testing, the only sign suggestive of oculomotor involvement was the dilated right pupil, fixed to light. At autopsy he was found to have an old area of extensive hemorrhage in the temporal lobe, which probably accounted for his convulsions, and a ruptured aneurysm of the posterior communicating artery.

Treatment.—This series is too small for an adequate evaluation of treatment. Poppen [2] stated that a small aneurysm arising from the posterior communicating artery can be either excised or trapped. If, however, the aneurysm involves the entire artery, surgical trapping or excision can only meet with disaster. In Case 4 the posterior communicating artery aneurysm was isolated by silver clips and the patient

14. (*a*) List, C. F., and Hodges, F. J.: Intracranial Angiography: Diagnosis of Vascular Lesions, J. Neurosurg. **3**:25, 1946. (*b*) Hodes, P. J.; Perryman, C. R., and Chamberlain, R. H.: Cerebral Angiography, Am. J. Roentgenol. **58**:543, 1947. (*c*) Lima, P. A.: Cerebral Angiography, New York, Oxford University Press, 1950.

15. Hamby, W. B.: Aneurysmal Origin of Nonfatal Subarachnoid Hemorrhage, J. Neurosurg. **10**:35, 1953.

made an uneventful recovery. Subarachnoid hemorrhage complicated the fifth case, and the common carotid artery was ligated in an effort to control the bleeding. It was recommended that the patient have a ligation of the aneurysm, but this she refused. At discharge she had a complete external and internal ophthalmoplegia with sparing of the abducens nerve. The headache, however, was gone. In one case (Case 1) surgery could not be attempted because the patient, in addition to the cerebral aneurysm, had an aortic aneurysm. Another patient had massive subarachnoid and intraventricular hemorrhage and was therefore unable to undergo surgery (Case 3). One patient (Case 2) had hemiparesis and aphasia following the arteriographic study, and the hemiparesis persisted.

CONCLUSIONS

Five additional cases of posterior communicating artery aneurysm are reported.

The most consistent clinical features of the unruptured aneurysm are unilateral retro-orbital pain and oculomotor nerve paralysis, usually beginning with ptosis of the eyelid and dilatation of the pupil, which is fixed to light and in accommodation, then progressing to paralysis of the other muscles supplied by this nerve.

When other cranial nerves are involved, the lesion is more likely to be an internal carotid artery aneurysm.

If the posterior communicating artery aneurysm ruptures, it may then show involvement of other cranial nerves, especially the trochlear, the abducens, or the ophthalmic branch of the trigeminal nerve.

On the other hand, if only the oculomotor nerve is involved, it is not possible clinically to differentiate between an internal carotid and a posterior communicating aneurysm, but angiography may help.

GENETIC ASPECTS OF MULTIPLE SCLEROSIS

RAGNAR MÜLLER, M.D.
STOCKHOLM

DISCUSSION of the etiology of multiple sclerosis has repeatedly aroused the speculation that genetic, constitutional factors might be involved. Considerable interest has therefore been accorded to reports of the occurrence of the disease in several members of the same family. As long as these reports are confined to the histories of a number of "familial" cases, their value as proof is extremely limited. This applies even when the author gives the percentage number of "familial" cases in a certain group of patients. If a satisfactory genetic study of the disease is to be made, it is necessary to investigate its incidence among the relatives of the affected persons (the probands) or to make studies of twins. Two investigations of the former kind have been made (Curtius and Speer,[1] 1937; Pratt, Compston, and McAlpine [2] (1951), and one of the latter (Thums,[3] 1939).

Curtius and Speer [1] made a personal examination of the parents and siblings of 106 patients with multiple sclerosis. They found no definite case among the parents but identified four cases among the 444 siblings. The incidence of the disease among the relatives, thus, was 0.61%; this was compared with the incidence of 0.023% given by Ackermann [4] for the population of Switzerland. The authors expressed the opinion that they had demonstrated a genetic, specific disposition to multiple sclerosis. However, judging from the case reports, the diagnosis was not conclusive in the cases of any of the four relatives affected. In two of these cases (Fam. II 22; Fam. II 41) the diagnosis was even extremely questionable.

Pratt and associates [2] based their investigation on 310 patients with multiple sclerosis. They found 15 secondary cases in the immediate families; 3 of them were of parents and 12 of siblings. The number of siblings was known for 168 patients only. These patients had 538 living siblings over the age of 15 years. Five of them had multiple sclerosis; the incidence thus was 1:108. The authors did not ascertain the number of parents alive at the time of the investigation but confined themselves to calculations, which resulted in the figure 465. The incidence of multiple sclerosis among the parents would, then, be 3:465, i. e., 1:155. The morbidity rate for the

From the Neurological Clinic of Serafimerlasarettet (Head, Prof. N. Antoni) and The Psychiatric Clinic of Karolinska Sjukhuset (Head: Prof. T. Sjögren).

1. Curtius, F., and Speer, H.: Multiple Sklerose und Erbanlage, Ztschr. ges. Neurol. u. Psychiat. **160**:226-245, 1937.

2. Pratt, R. T. C.; Compston, N. D., and McAlpine, D.: The Familial Incidence of Disseminated Sclerosis and Its Significance, Brain **74**:191-232, 1951.

3. Thums, K.: Das Erblichkeitproblem bei der multiplen Sklerose, Munchen. med. Wchnschr. **86**:1634-1638, 1939.

4. Ackermann, A.: Die multiple Sklerose in der Schweiz, Schweiz. med. Wchnschr. **61**:1245-1250, 1931.

general population was calculated on the basis of the official statistics for the number of deaths from multiple sclerosis in England and Wales between 1937 and 1946. The mean duration of the disease was estimated at 18 years. The calculations gave an incidence of 1 : 2,564, but since the disease only infrequently attacks persons less than 15 years of age, the authors gave an incidence of 1 : 2,000 for the population above this age. The observed incidence of the disease among the relatives of the probands was thus higher than that which could be expected from the incidence in the general population. The authors concluded that "there is a small but nevertheless significant familial incidence of disseminated sclerosis." The importance of this observation was discussed, and the opinion was expressed that "a genetic factor is present in disseminated sclerosis and that there is evidence pointing to both a dominant and a recessive mode of inheritance."

Thums [3] assembled a representative series of twins from various hospitals. There were 96 patients with multiple sclerosis in the series. Attempts to trace the twins of these patients disclosed that 35 of them had died before the age of 5 years. No information regarding the twin could be obtained in two cases. Thus, 59 pairs of twins remained for the investigation. At the time of publication, 50 pairs had been examined; 14 of them were monozygotic. All the monozygotic pairs of twins were discordant with respect to multiple sclerosis. One twin had, however, died at the age of 21 years. Of the rest, nine were over 40 years of age, 2 were between 35 and 40 years of age, and two were younger. With the exception of one uncertain case, the dizygotic pairs of twins were also discordant with respect to the disease. It may be stressed that Thums examined the twins in his series personally on at least two occasions at an interval of several years. He stated that he had demonstrated that genetic factors play an unimportant role in multiple sclerosis and that the disease *im wesentlichen eine Umweltkrankheit ist.*

MATERIAL AND METHOD

There were 750 patients in the present series, consisting of most of those in an original series of 810 patients. A detailed account has been given of the composition of this series and of the principles according to which it was assembled (Müller,[4a] 1949). It may be denoted as a representative sample of persons in the general population of Sweden with multiple sclerosis. The 750 probands were treated for multiple sclerosis during a 25-year period at the neurological clinic of Serafimerlasarettet in Stockholm and at the medical clinic of the University Hospital of Uppsala. Both inpatients and outpatients were included.

In 1946, I visited and examined the 569 probands who were still alive. The relatives living with the probands were examined at the same time. Detailed information was obtained about the state of health of the other relatives and about the illnesses undergone by relatives who were dead. The main interest was focused on the immediate family: parents, siblings, and children. When the proband had died before 1946, I visited two or more of the close relatives in order to obtain the necessary data. I subsequently made a personal examination of most of those relatives whom I had not met during the investigation but who, judging by the information given, could be suspected of having had, or of having, an organic nervous disease. In addition, information was obtained from the physicians who had attended them, as well as copies of the case reports from hospitals at which they had been treated. When such a relation had died, a copy of the death certificate was procured from the parish register.

In the publication already mentioned (Müller[4a]) an account was also given of the criteria for the diagnosis used in the series of probands. It may be extremely difficult to differentiate

4a. Müller, N.: Studies on Disseminated Sclerosis with Special Reference to Symptomatology, Course and Prognosis, Acta med. scandinav., Supp. 222, 1949.

TABLE 1.—*Clinical Data on the Proband Families with More than One Affected Member*

Family	Relationship to Affected Relative	P; S*	Age at Onset, Yr.	AE†	Living or Dead	Autopsy	Relationship to Affected Relative	P; S*	Age at Onset, Yr.	AE†	Living or Dead	Autopsy	Relationship to Affected Relative	P; S*	Age at Onset, Yr.	AE†	Living or Dead	Autopsy
A	Mother	P	32	58	L	..	Daughter	P	22	26	L	..	.....	..	..	..	..	..
B	Mother	P	30	75	L	..	Daughter	P	34	36	L	..	.....	..	..	..	..	..
C	Mother	P	47	58	L	..	Son	P	27	30	L	..	.....	..	..	..	..	..
D	Daughter	P	14	26	L	..	Mother	S	29	38	D	+	.....	..	..	..	..	..
E	Daughter	P	21	40	L	..	Father	S	33	47	D	+	.....	..	..	..	..	..
F	Brother	P	25	50	L	..	Brother	P	21	47	L	..	Daughter	S	18	21	L	..
G	Brother	P	30	30	D	—	Brother	P	17	26	D	—	.....	..	..	..	..	..
H	Brother	P	31	43	L	..	Brother	S	25	51	L	..	.....	..	..	..	..	..
I	Brother	P	21	33	L	..	Brother	S	28	28	L	..	.....	..	..	..	..	..
J	Brother	P	41	44	L	..	Brother	P	29	36	L	..	Sister	P	19	30	D	—
K	Brother	P	23	49	L	..	Sister	P	33	38	L	..	.....	..	..	..	..	..
L	Brother	P	23	44	D	—	Sister	S	19	34	D	—	.....	..	..	..	..	..
M	Brother	P	28	43	L	..	Sister	S	31	47	L	..	.....	..	..	..	..	..
N	Brother	P	21	33	D	—	Sister	P	19	32	D	—	.....	..	..	..	..	..
O	Sister	P	39	42	L	..	Sister	P	28	38	L	..	.....	..	..	..	..	..
P	Sister	P	21	26	L	..	Sister	P	19	20	L	..	.....	..	..	..	..	..

* P indicates proband; S, secondary case.
† AE indicates age at end of observation period

clinically between multiple sclerosis and certain other organic nervous diseases, such as the spinocerebellar ataxias (Sjögren,[5] 1943). No cases in which the diagnosis was questionable were, however, included. The same strict requirements for the reliability of the diagnosis were applied in the investigation of the relatives. Knowledge of the disease in the proband was not allowed to influence the evaluation. In a few instances the diagnosis was verified at autopsy.

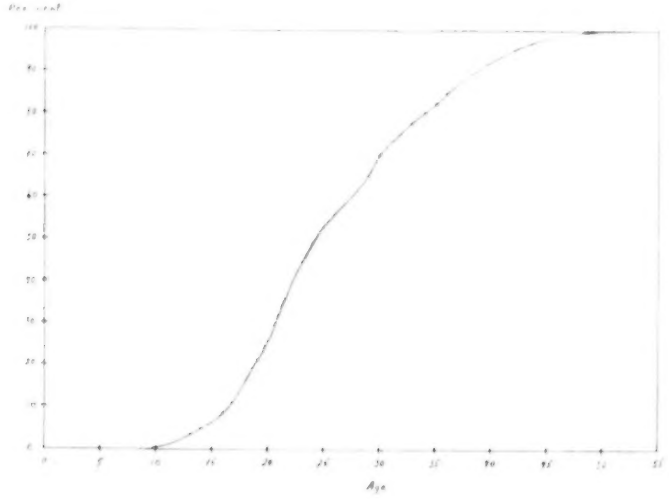
Strömgren's "exact" method was used for the genetic-statistical calculations. This involves the calculation of the weight of each person with regard to the risk of becoming affected during the time he has been under observation. The weight (V_x) of an unaffected person at x years of age is then

$$V_x = \frac{\text{Probability of becoming affected before the age of } x \text{ years}}{\text{Probability on the whole of becoming affected}}$$

The observed number of affected persons among the relatives is divided by the reduced number of members of the families obtained with the aforementioned system of weights. The resulting figures are then analyzed in view of different modes of inheritance.

Reference is made to Alström[6] for a more detailed account of the calculations.

The chart shows that part of the risk of becoming affected, expressed as a percentage, passed at a certain age.



Morbidity risk in relation to the age of survival.

RESULTS

In the series of 750 probands, 27 had some close relative (parent, sibling, or child) suffering from multiple sclerosis. Four probands had two affected relatives, and 23 had one affected relative. It must be mentioned that several of the probands were consanguineous. The 27 probands with an affected relative were thus distributed among 16 families (Families A to P) (Table 1). In accordance with Weinberg's proband method, all the persons in the series were counted as probands, irrespective of their relationship. In a pair of siblings, for example, each sibling was treated both as a proband and as a sibling.

5. Sjögren, T.: Klinische und erbbiologische Untersuchungen über die Heredoataxien, Acta psychiat. et neurol., Supp. 27, 1943.

6. Alström, C. H.: A Study of Epilepsy in Its Clinical, Social, and Genetic Aspects, Acta psychiat. et neurol. Supp. 63, pp. 1-284, 1950.

Of the 27 probands with an affected relative, 14 were women and 13 men. There was also a slight excess of women in the whole series of probands. For 14 of the 27 probands (52%) the age of onset was before 25; for 2 it was after the age of 40. In the series as a whole, 52% of the probands became affected before the age of 25, and 8%, after the age of 40.

A comparison of the "familial" and the other cases in the series of probands with respect to the symptoms and the course of the illness disclosed no difference of any consequence.

Table 2 shows the observed and weighted number of members in the various categories of relatives, as well as the number of affected members of the probands' families.

The incidence of multiple sclerosis among the parents, siblings, and children of the probands (weighted figures) is recorded in Table 3. It is seen that the incidence

TABLE 2.—*Observed and Weighted Figures of Probands' Relatives; Observed Number of Relatives with Multiple Sclerosis*

Number	Parents	Siblings	Children
Observed	1,403	2,815	692 ≥ 10 yr. old
Weighted	1,478	2,268	172
Affected relatives	5	22	4

TABLE 3.—*Percentage Incidence* of Multiple Sclerosis in the Probands' Relatives*

Parents	0.3 ± 0.15
Siblings	1.0 ± 0.21
Children	2.3 ± 1.15
Total	0.8 ± 0.14

* The incidence is calculated on the weighted number.

is not the same in the three categories. The number of those affected is, however, small, particularly among the parents and children; the random variations are therefore large.

A calculation of the incidence of affected members in the whole group of observed relatives over the age of 9 years gives a percentage figure of 0.6 ± 0.11.

COMMENT

Studies of the incidence of multiple sclerosis in the general population have hitherto been made according to one of two principles. Inquiries have been made of practicing physicians, hospitals, and other such institutions in a certain region in order to ascertain the number of cases in which the diagnosis was made. Or, the number of deaths from the disease have been determined from the official statistics.

The latter method, which was used by Pratt and associates, among others, is, presumably, the less exact. It cannot be expected that in every case of multiple sclerosis the diagnosis will be given on the death certificate. Many patients with multiple sclerosis die of an intercurrent disease. The attention of the physician called in to treat this last illness is less likely to be focused on the disease of the

nervous system. Many patients are not under the care of a neurologist at the time. The nervous disease, therefore, is not infrequently omitted from the death certificate or is recorded under an incorrect diagnosis. This is at any rate the case in Sweden, and the experience in the United States gives the same indication (Ipsen,[7] 1950). Another factor which decreases the value of the method is the lack of exact information regarding the duration of the disease.

Weaknesses are also inherent in the former method, in which the morbidity figures are ascertained by means of the records of physicians and hospitals. This method has been used by Ackermann [8] Sällström,[9] Ipsen,[7] and Kurland,[10] among others. Multiple sclerosis is a relatively uncommon disease, which may be difficult to diagnose clinically in the early stages. Specific clinical manifestations and laboratory tests are lacking. Unless the physician is familar with the disease, he may fail to diagnose it until the classic picture of symptoms has developed. Nor is it uncommon for the patient to seek medical advice only many years after the onset, since initially there is a strong tendency to spontaneous remission. The morbidity figures obtained with this method are, therefore, probably too low. Ipsen and Kurland found an incidence of 0.04 and 0.05%, respectively, in certain regions of the United States and Canada. The aforementioned sources of error are of less importance if, like Kurland, one wishes to compare the incidence of the disease in different populated areas and the same method is used throughout. On the other hand, the figures for the incidence found in this way cannot be compared with those obtained by means of investigation of the relatives of a group of patients. The relatives are then subjected to such close attention and thorough examination by a neurologist that it is scarcely likely that any case will be overlooked.

Even if the morbidity figures for a cross section of the general population were available, it would not be possible to make a direct comparison of them and the corresponding figures for the relatives of the patients, because the age distribution in the latter category differs from that in the general population and the risk of becoming affected varies with the age.

The incidence of multiple sclerosis at a certain age is not known, as it is, for example, in epilepsy. The incidence of epilepsy at military call-up age is known; it is therefore possible to compare this incidence with that for the relatives of the probands at the corresponding age (Alström[6]).

In the present series, the incidence of multiple sclerosis among the observed relatives of the probands over 9 years of age is $0.6 \pm 0.11\%$. In view of the facts already mentioned, it cannot be stated definitely that this incidence is higher than that which may be expected on the basis of the morbidity in the general population, but this is presumably the case. It cannot, however, be ruled out that some case of a "hereditary degenerative disorder" may have been accidentally included, despite the strict criteria for the diagnosis and the thorough clinical analysis. It must be recalled that postmortem examination was made in only a few cases.

7. Ipsen, J.: Prevalence and Incidence of Multiple Sclerosis in Boston 1938-1948: Preliminary Report, Arch. Neurol. & Psychiat. **64**:631-640, 1950.

8. Footnote deleted.

9. Sällström, T.: Das Vorkommen und die Verbreitung der multiplen Sklerose in Schweden, Acta med. scandinav., Supp. 137, 1942.

10. Kurland, L. T.: Frequency and Geographic Distribution of Multiple Sclerosis as Indicated by Mortality Statistics and Morbidity Surveys in the United States and Canada, Am. J. Hyg. **55**:457-476, 1952.

There is reason, nevertheless, to test whether the incidence of the disease among the parents, siblings, and children of the probands in the present series is in accordance with the hypothesis of any particular mode of inheritance.

Multiple sclerosis is a rare disease. If it followed a monohybrid recessive mode of inheritance, an increased incidence of consanguineous marriages among the probands' parents could be expected. The incidence in the present series is 2.2 ± 0.68%. The corresponding incidence in the general rural population in Sweden is 2 to 3% (Sjogren,[11] 1948). If multiple sclerosis is still to be envisaged as a recessively determined disorder, it is necessary to postulate a low degree of manifestation —in the present series less than 10%.

The existing difference in the incidences of multiple sclerosis in the respective categories of relatives may be explained on the grounds of random variations. The difference between the incidence in the parents and that in the children does not amount to twice the standard error. It is also possible that the probands' statements about their children were more accurate than those about their parents. Many of the latter were dead at the time of the investigation. If it is assumed that no real difference exists between generations with regard to the incidence of the disease, a dominant mode of inheritance might be postulated. In this case, the degree of manifestation must, in view of the incidence of the disease in the respective categories of relatives, be extremely low, i. e., less than 5%.

Alstrom[9] has thoroughly discussed the principles of the concept of inhibition of manifestation. He found that this hypothesis should be applied in human genetics only with the greatest caution, not least with postulated recessivity and a low morbidity rate among the siblings. He stated:

> It is best to refrain from a genetic explanation when resort must be made to such an auxiliary hypothesis as an inhibition of manifestation of the main gene from environmental factors, which must exceed 90%.

Obviously, there is the possibility that the low degree of manifestation might be due to modifying genes which inhibit the effect of a dominant major gene. Such a hypothesis would be difficult to substantiate and is too far-fetched to be acceptable.

A review of the entire literature revealed only a few reports of families in which more than two siblings were affected. This speaks against the assumption that multiple additive genetic factors are active.

It is evident from the foregoing, as well as from the results of Thums's studies on twins, that the available data afford no support to the concept of multiple sclerosis as a hereditary disease in the true meaning of the term.

Even if it is assumed that the incidence of the disease is higher among the relatives of persons with multiple sclerosis than in the general population, the difference must be so small that it constitutes no proof of the occurrence of genetic factors. Moreover, of the 750 probands in the present series, only 27 (3.6%) had an affected relative (parent, sibling, or child). This does not imply that genetic factors, in the wider application of the term, lack importance. In the case of tuberculosis, for example, the hypothesis has been advanced that resistance to the disease is genetically determined. Such a hypothesis might also be applied in multiple sclerosis. At present, however, nothing is known of the etiology of the latter disease.

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11. Sjögren, T.: Genetic-Statistical and Psychiatric Investigation of a West Swedish Population, Acta psychiat. et neurol., Supp. 52, pp. 1-102, 1948.

It is even possible that several different diseases are now classified under the term multiple sclerosis. A better understanding of these problems must be reached before a more factual discussion of the genetic conditions in multiple sclerosis can be entered into.

SUMMARY

The present series consists of 810 patients (probands) with multiple sclerosis.

The incidence of the disease in the probands' parents was $0.3 \pm 0.15\%$, in the siblings $1.0 \pm 0.21\%$, and in the children $2.3 \pm 1.15\%$. The calculations are based on Strömgren's "exact" method.

The incidence of the disease in all the observed relatives over the age of 9 years was found to be $0.6 \pm 0.11\%$.

Only 27 probands (3.6%) had some close relative (parent, sibling, or child) affected with multiple sclerosis.

The extent to which different genetic hypotheses are in agreement with the morbidity rate in the close relatives of the probands was investigated. The available data gave no support to the concept that genetic factors are active in multiple sclerosis.

SYRINGOMYELIA

A Clinicopathologic Study

MARTIN G. NETSKY, M.D.
NEW YORK

AT THE turn of the century it was well recognized that cavitation in the spinal cord occurs in association with a variety of causative agents. Schlesinger,[1] in his monograph, cited cavities occurring as a result of traumatic hematomyelia; softenings of inflammatory and noninflammatory origin, and cavities resulting from malformations, tumors, gliosis, and vascular changes associated with gliosis. In later years, other neurologic conditions have been shown to be associated with the clinical features of syringomyelia and the pathologic picture of cavitation. Among these disorders are the Arnold-Chiari malformation, platybasia, the Klippel-Feil syndrome, and, more recently, herniation of cervical intervertebral discs.

Little has been added to the clinical picture or to the understanding and treatment of syringomyelia other than to separate the described conditions from what is called "true" syringomyelia. In this paper eight cases with necropsy are presented to demonstrate some new considerations of this disorder.

THE DEVELOPMENT OF THE SPINAL CORD AND CENTRAL CANAL

This material is taken largely from Streeter.[2] It is presented because of the importance of embryonic development in most theories of the origin of syringomyelia.

The first evidence of the nervous system is in the neural groove. The elevation of the edges and their approximation and fusion across the midline to form the neural tube occur in the first two weeks. Formation of the neural tube is then most advanced in the middle of the germ plate, corresponding to the junction of the brain and the spinal cord. From this region, differentiation and closure of the tube extend caudally and orally. While still in the neural-plate stage, before its closure, the central nervous system is divided into an anterior portion, which is to form the brain, and a posterior portion, which is to form the spinal cord. The spinal cord portion is narrower and more uniform in width. Most of the spinal portion of the neural tube at this stage is that which is to form the cervical part of the cord. The lower part of the cord is formed by the caudal expansion of the neural plate. In the third and fourth weeks, the third, or cervical, flexure is formed, in consequence of unequal growth of different parts of the neural tube. At the end of the first month the spinal cord is largest in the cervical region and from there gradually tapers down to the

Aided by a grant from the Sandy Schneider Memorial Fund.

From the Laboratory and Neuropsychiatric Division, Montefiore Hospital for Chronic Diseases.

1. Schlesinger, H.: Die Syringomyelie, Vienna, Franz Deuticke, 1902.

2. Streeter, G. L.: The Development of the Nervous System, in Manual of Human Embryology, edited by F. Keibel, and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1912.

coccyx, except in the lumbosacral region, where it is again somewhat larger. The tendency toward cervical and lumbar enlargement is plainly indicated. The cord in cross section consists principally of two thick lateral walls, which are united in the midline ventrally and dorsally. These points of union are reduced to thin seams. The cells on either side form a marginal, a mantle, and an ependymal zone. The dorsal roof plate and the ventral floor plate retain their primitive characteristics and are modified only secondarily, owing to the changes in the adjoining portions of the lateral walls. The lateral walls undergo vigorous growth, and this largely determines

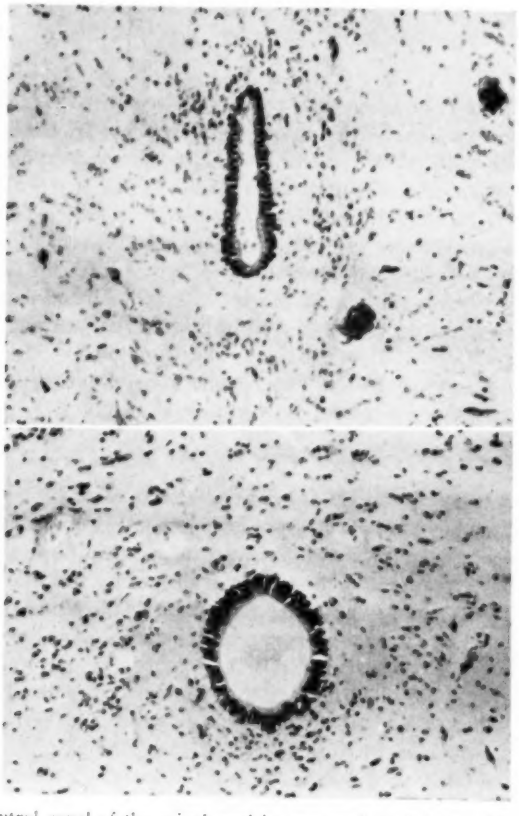

Fig. 1.—The central canal of the spinal cord in two newborn infants without neurologic disorder. There is a single layer of ependymal cells with a patent, round or oval canal. Nissl technique; × 120.

the shape of the cord. At the beginning of the second month (15-mm. stage) the lumen of the cord is still relatively large. From that time on, until the embryo is 80 mm. in length, the lumen decreases in actual size, and still more so in size relative to that of the cord. At the 15-mm. stage the lumen is an elongated oval slit in transverse section and is wider in the dorsal half. At 30 mm. the condition is reversed, and the dorsal portion is reduced to a narrow slit. Eventually, the dorsal portion becomes obliterated, and there remains only the round or oval portion of the central canal.

The ependymal cells that form the ventral portion of the lumen in the 15-mm. stage differ from those forming the dorsal portion. The process of proliferation remains active in the dorsal portion. In embryos of from 15 mm. on, there is a

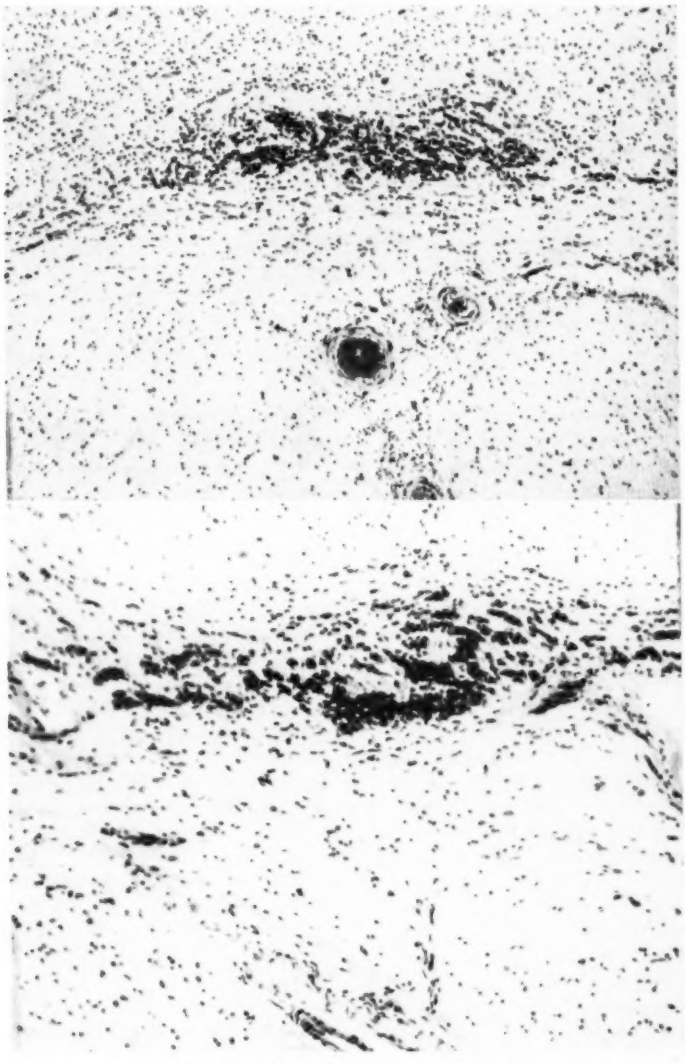

Fig. 2.—Two examples of the proliferated central canal in adults who died of non-neurologic disorders. Nissl technique; *A*, × 60; *B*, × 120.

gradual subsidence of proliferation of ependymal cells around the dorsal portion, and the whole ependymal border comes to a resting stage. The border then forms a narrow, sharply demarcated edge—the central canal. The extension of the seam of closure forms the posterior median septum.

In the present study, examination of the central canal in 24 infants, of ages ranging from a few hours to 14 months, revealed that in all instances there was a single layer of cuboidal epithelium forming a central canal, which was usually round or oval (Fig. 1). This contrasts strikingly with the appearance of the central canal in adults. A study by Cornil and Mosinger[3] of 66 normal cords revealed that only 19 (29%) had a patent canal. The remainder (71%) had central canals that were partially or totally obliterated. A review of 50 normal adult spinal cords from the Montefiore Hospital files confirmed this except that the incidence of patent canals lined by a single layer of epithelium was lower. In 80% of the cords studied here the central canal was obliterated by proliferation of ependymal cells, usually in a disorderly fashion without formation of recognizable lumens (Fig. 2). These ependymal cells in some cases extended laterally from the usual position of the central canal along the line of gray matter into the ventral portion of the posterior horns. The individual ependymal cells in many instances were separated by glial fibrils, or the cells lay in small clusters. In some instances they grew to sufficient size to form a benign and asymptomatic mass.

These findings indicate that some of the changes of ependyma described in syringomyelia as congenital rests are actually acquired variations. The demonstration of a syrinx in association with proliferated ependyma, therefore, does not furnish evidence of the cause of the cavitation and does not imply a congenital origin of the disorder. Cavitation may occur at a distance from ependyma or may be in association with it, and syringomyelia may occur with or without hyperplasia of ependyma.

REPORT OF CASES

Case 1.[4]—J. W., a man aged 48, a painter, noticed sharp, sticking pains in the left wrist and fingers early in 1920. Four weeks later there were dull aching pains in the right arm and shoulder. In June he experienced occasional diplopia, and in August he complained of "pressing pains" in the abdomen and back. The right arm slowly and progressively became weak. Three months later the patient noticed a "heavy sensation" in the right calf. In a few weeks there was a sensation which he described as being "as if something grabbed my left leg." The lower extremities then slowly became weak. In January, 1921, he had "cutting pains" in the right flank, which lasted a day. The right leg occasionally moved involuntarily. Examination at a hospital in February, 1921, revealed the following positive findings: tortuosity of retinal vessels; inequality of the pupils, the left pupil being smaller than the right; left facial weakness; weakness and wasting of the right biceps, right triceps, and right pectoralis major muscles; diminished triceps and biceps reflexes; active knee and ankle reflexes; a bilateral Babinski sign and absence of abdominal skin reflexes, and sensory changes involving temperature sensation, as shown in Figure 3*A*. Loss of other types of sensation was not indicated. There was a painless ulcer on the right shoulder. The cerebrospinal fluid contained 3 lymphocytes per cubic millimeter, and the Wassermann reaction was negative. A diagnosis of syringomyelia and syringobulbia was made.

He was admitted to Montefiore Hospital in May, 1921. An additional historical detail was the existence of dorsal kyphosis for as long as the patient could remember. Examination revealed moderate dorsal kyphosis and scoliosis. There were fascicular twitches of the muscles of the forearms. Generalized weakness and atrophy were present in both upper extremities, mostly on

3. Cornil, L., and Mosinger, M.: Sur les processus prolifératifs de l'épendyme médullaire (rapports avec les tumeurs intramédullaires et la syringomyélia), Rev. neurol. **1**:749-754, 1933.

4. Cases 1 and 6 have been reported by others with a different interpretation (Davison, C.; Brock, S., and Goodhart, S. P.: Atherosclerotic Myelopathy with Syrinx Formation: Differentiation from Other Types of Syringomyelia, Arch. Neurol. & Psychiat. **50**:565-574, 1943).

the right. The patient was able to walk, although the gait was slightly spastic. The deep reflexes were diminished in the upper extremities, to a greater extent on the right, and were exaggerated in the lower extremities. There was a bilateral Babinski sign. The left pupil was smaller than the right, but both reacted to light and in convergence. Facial weakness was not confirmed. Touch sensation was intact as was muscle and joint sensibility. Vibration sensation was lost except on the forehead. Loss of pain and temperature sensibility was then more extensive (Fig. 3*B* and *C*). Because of the rapid progression of the disorder and the initial pains of presumed root character, the presence of an intramedullary neoplasm of the cervical cord was considered, but the diagnosis of syringomyelia was finally made. These diagnoses were based on the presence of fasciculations, dissociated loss of pain and touch sensation, pyra-

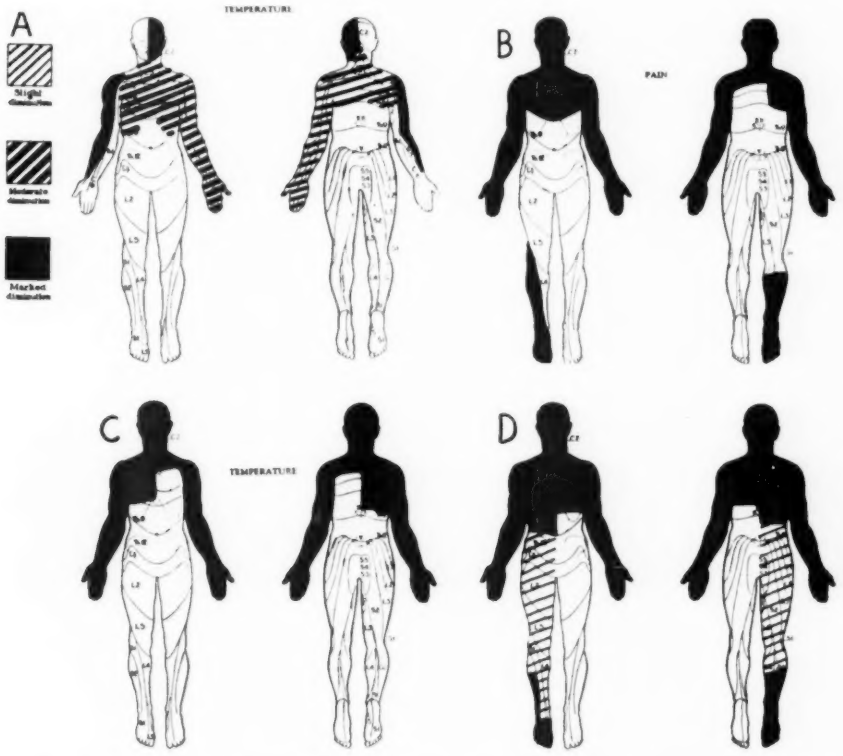

Fig. 3 (Case 1).—*A*, alteration of temperature sensation in March, 1921. The severity of the sensory loss is indicated in the key, which applies to all successive diagrams. *B* and *C*, alteration of pain and temperature sensation in May, 1921. See text. *D*, alteration of pain and temperature sensation in March, 1936. Note that there has been little progression since May, 1921.

midal tract signs, and kyphosis; but the ultimately slow development of the disease made syringomyelia more likely.

Roentgenograms of the skull revealed small, irregular zones of bone rarefaction in the parietal and occipital regions. There were no alterations of the cervical spine. The patient received radium therapy, 9,000 mc-hr. to the cervical region from October, 1921, to July, 1922. There was no objective change in his condition, but he thought that severe pains on the right side of the body were diminished after treatment. Nevertheless, the pains continued, and another treatment was given in 1923. The patient stated that he felt much better when receiving radium

treatment. The objective findings in 1924 were, however, no different than on admission. Roentgen therapy was given to five portals in the cervicodorsal region in 1926, 1927, and 1930. The patient still complained of intermittently severe pain over the right side of the body.

In 1928 examination revealed spastic paraparesis with bilateral pyramidal tract signs. There was almost complete paralysis of the right upper extremity, but motor power was fairly good on the left. Fasciculations were still present in the upper extremities. There was analgesia above the sixth thoracic level, including the face; but it was noted that the buccal and nasal mucous membranes were spared. Vibratory sense was still absent below the clavicles, and position sense remained intact. The tip of the tongue was atrophied, with fasciculations. The patient stated he did not feel better or worse than in 1921.

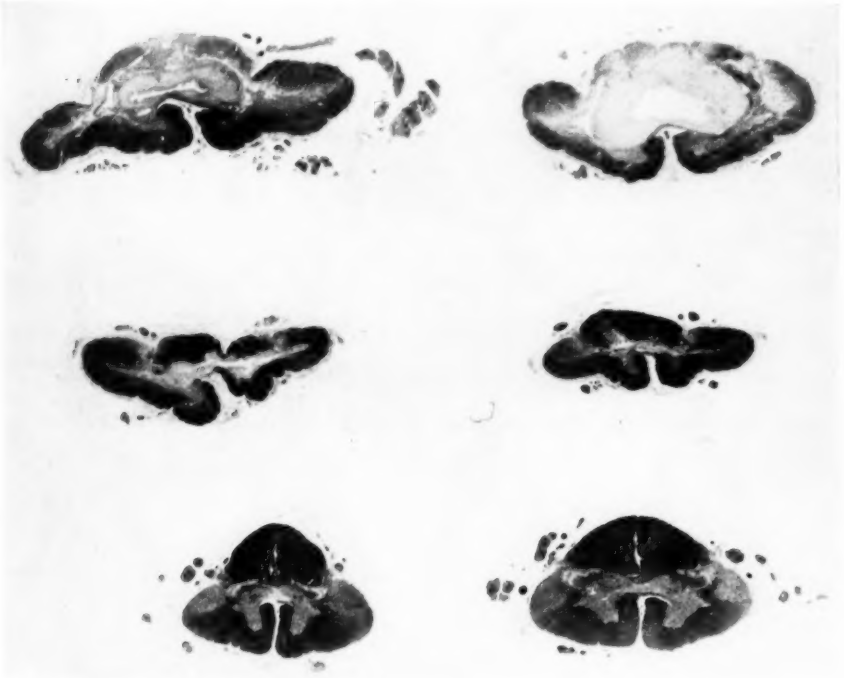

Fig. 4 (Case 1).—The large cavity in the cervical region becomes small at thoracic levels. A few large blood vessels can be seen in the upper left-hand section with this magnification. There is descending demyelination in the thoracolumbar segments. Weil technique; × 4.5

Examination in 1930 revealed fasciculations in the muscles of both thighs but retention of some motor power in the lower extremities. Touch sensation was still intact, and vibration, pain, and temperature sensations were lost, as before. At this time he made a few errors in determining the position of the toes of the right foot. Mucous membrane sensation was normal, despite loss of sensation on the face. In 1936, the lower extremities became stiffer, and there was increasing weakness in the legs. There were pains on the right side of the abdomen and complaints of numbness and tingling in both hands. Examination in 1936 showed very little alteration except for a slight lowering of the sensory level on the chest and mild hypalgesia in the right leg (Fig. 3*D*). Lumbar puncture in 1936 failed to disclose evidence of block. The cerebrospinal fluid protein was 32 mg. per 100 cc.; there were 3 cells per cubic millimeter, and the Wassermann reaction was negative. An additional course of x-ray therapy was given, amounting to 2,000 r to each of four portals. The patient stated that there was marked relief

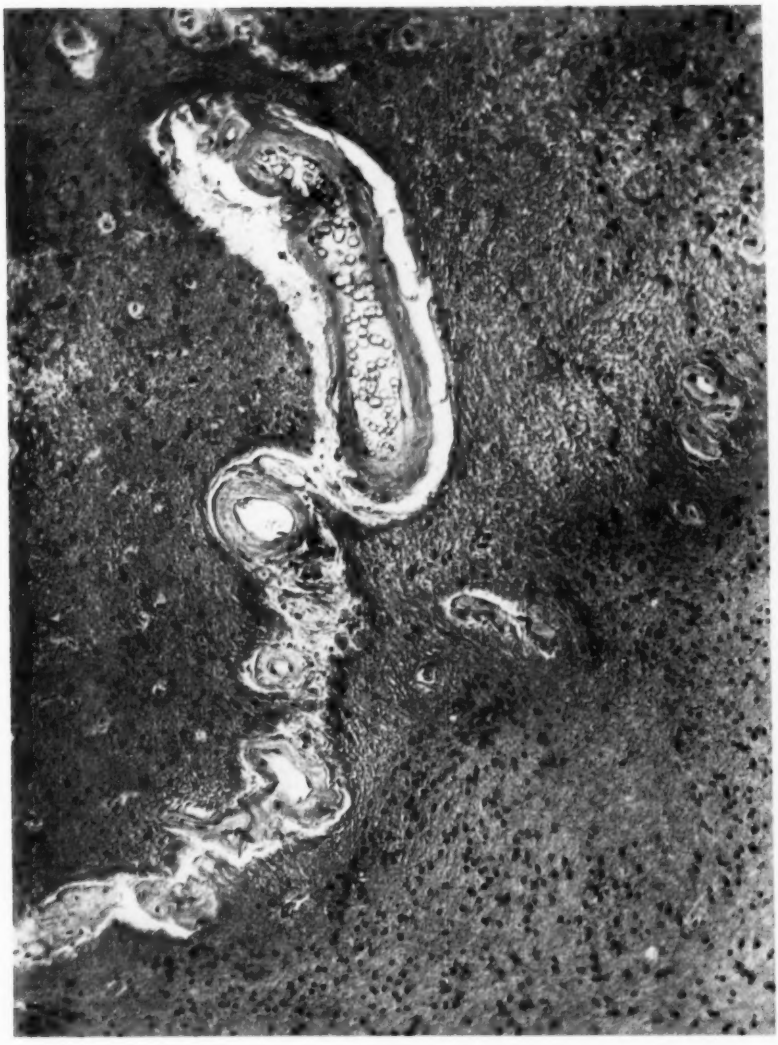

Fig. 5 (Case 1).—Large and small hyalinized, malformed blood vessels are seen in the spinal cord at the edge of reactive gliosis. The normal parenchyma is above and to the left; the glial reaction is below and to the right. Hematoxylin and eosin technique; × 120.

of pain after this. Thereafter, repeated bouts of pain on the right side occurred, but improved spontaneously without x-ray therapy. In 1938 definite impairment of position sense in the fingers and toes finally was noted. In February, 1941, the patient suddenly became pale and comatose, with cyanotic lips and gray color. The blood pressure was 70/45. He vomited about 500 cc. of coffee-ground material and died the same day. It was thought that he had a hemorrhage in the upper gastrointestinal tract. The duration of the neurologic disorder was 21 years.

Necropsy revealed a penetrating peptic ulcer with rupture into the splenic artery, and massive gastric hemorrhage. The brain was atrophic in the frontal region, and the vessels at the base were severely atherosclerotic. There was moderate uniform dilatation of the lateral ventricles.

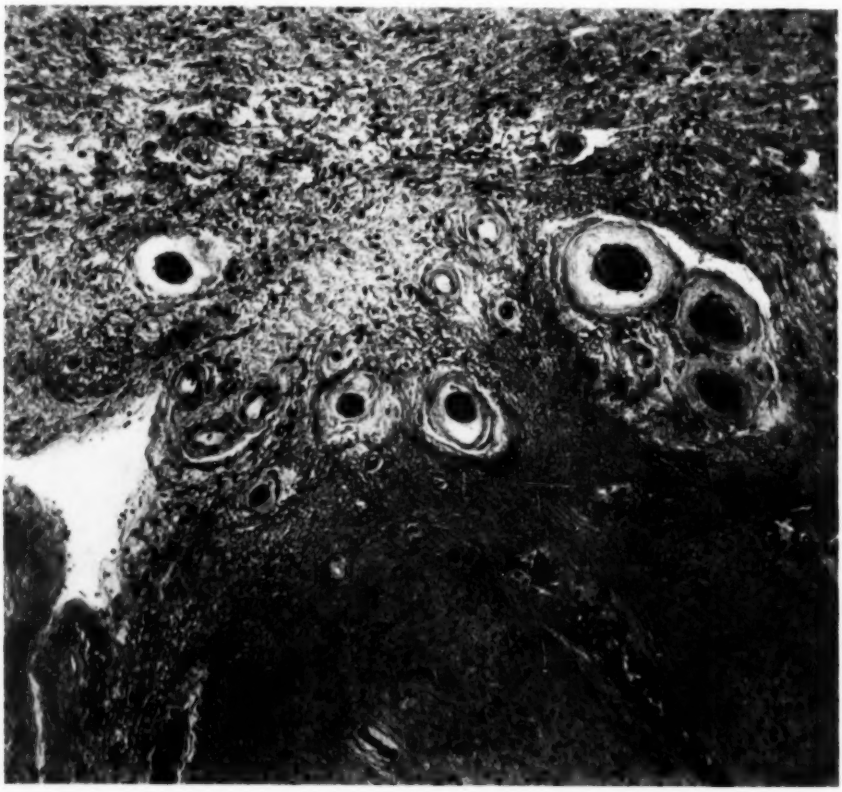

Fig. 6 (Case 1).—Characteristic clusters of malformed vessels of different sizes lie between the glial reaction and the parenchyma of the spinal cord. Hematoxylin and eosin technique; × 120.

A small focus of malacia was seen in the inner segment of the left globus pallidus. The aqueduct of Sylvius was dilated, but the fourth ventricle was normal in size. The spinal cord was thinner than usual. A large central cavity extended as far as the lower thoracic region, diminishing in size in the lower segments.

Microscopic examination revealed that the midcervical portion of the spinal cord contained a large mass with a central cavity and separate small cavities laterally situated (Fig. 4). There was demyelination of the midportion of the lateral funiculi and of most of the posterior columns. At this level the central canal was separate from the syrinx and contained clusters of ependymal cells. Small aggregates of ependymal cells were seen at short distances from the central canal.

The lining of the large cavity was a wavy band of connective tissue, resembling the internal elastica of a blood vessel. The surrounding tissue contained an orderly glial reaction. The separate small cavities were similar except that the immediate lining was glial and acellular. There were a few thick-walled blood vessels, but these probably could be accounted for as reactive phenomena. The posterior median septum was fused.

Lower in the cervical region the picture was similar except that the central cavity was larger. Many of the fibers of the ventral commissure were present, but the myelin sheaths were ballooned and generally altered. The posterior roots were intact. The anterior horns were compressed, and the neurons had disappeared or were shrunken. The acellular connective tissue band surrounding the central cavity contained numerous vascular spaces lined by endothelial cells. The cavity involved the commissural region without implicating the central canal. The

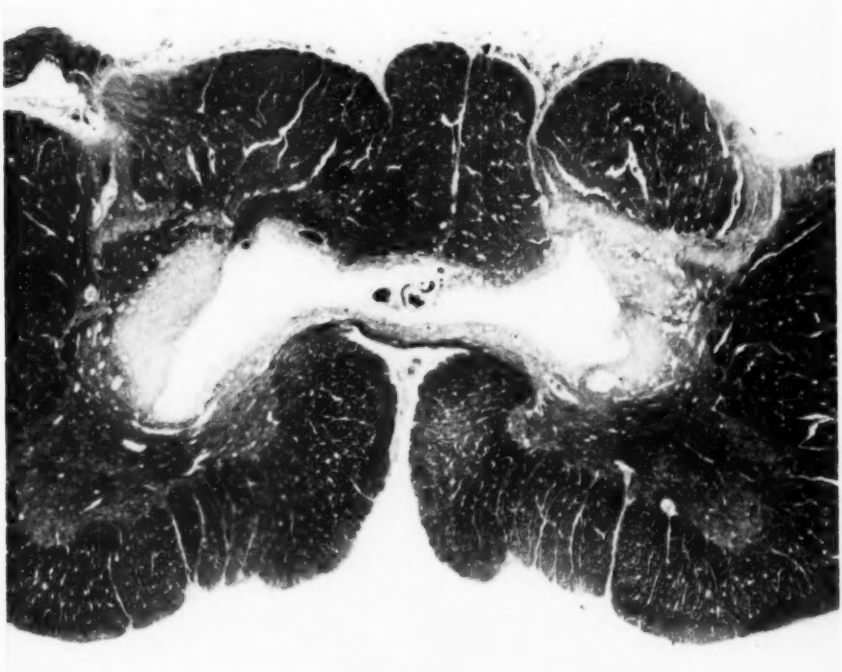

Fig. 7 (Case 2).—The large central cavity lies mostly within gray matter. Large malformed blood vessels can be seen in the cavity, and numerous smaller vessels lie scattered in and around the pale-staining gliotic zone. Weil technique; × 18.

anterior median fissure contained an excessive number of thick-walled, endothelium-lined blood vessels. In addition, there were numerous blood vessels in the syrinx and in clusters at the border of the gliotic process (Figs. 5 and 6). Some of these vessels were larger and more numerous than could be accounted for by a simple reactive process.

In the upper thoracic region the cavity grew smaller and was adjacent to, but independent of, the central canal. There were no ependymal lining cells in this region, but elongated endothelial cells formed the border. In the lumbar region a bilateral descending demyelination was seen. The central canal was composed of proliferated ependymal cells. Vascular abnormalities were lacking.

The small zone of malacia in the pallidum was old and cystic. It was bridged by many large blood vessels, none of which were occluded.

Comment.—The onset, with widely scattered, sharp pains for more than a year, is of interest. It is commonly considered that onset with pain is evidence of extramedullary disorder, but such complaints are not uncommon in cases of intramedullary disease.[5] This patient had a progressive illness lasting about two and one-half years, and thereafter his condition remained relatively stationary for almost 20 years of continuous hospitalization. Death was the result of a massive gastric hemorrhage. There was ultimately little doubt of the diagnosis clinically, most of the signs and

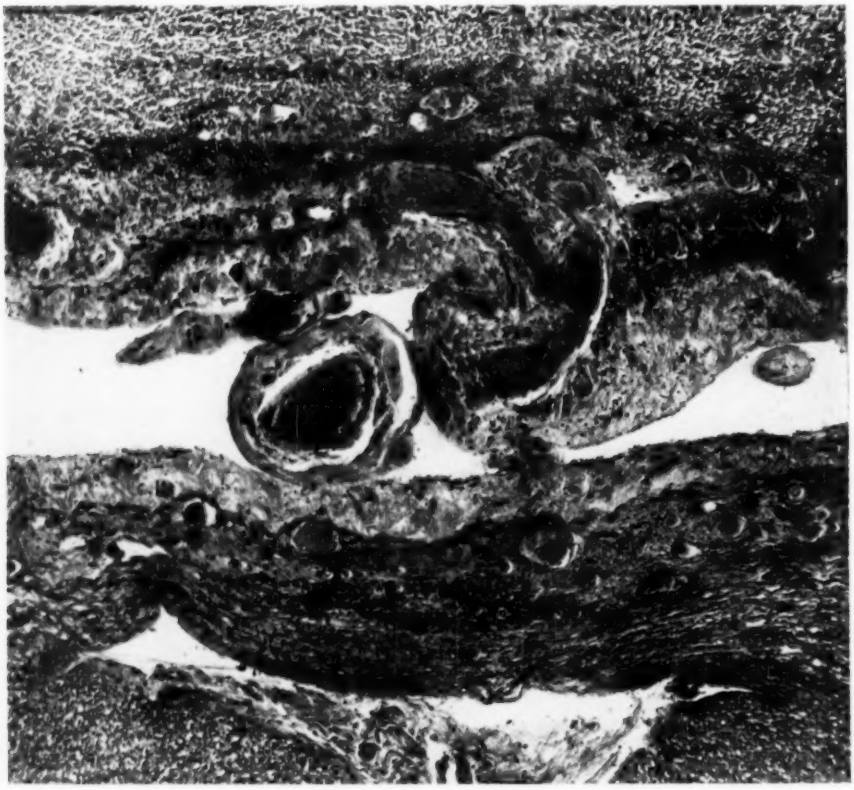

Fig. 8 (Case 2).—Higher-power view of the large vessels and connective tissue wall of the cavity shown in Figure 7. Note the scattered ependymal cells of the central canal, without a lumen. These are situated below the cavity. Hematoxylin and eosin technique; × 84.

symptoms of syringomyelia being present. The major problem in management was that of severe pain on the right side of the body. Both radium and x-ray therapy resulted in some subjective improvement, but this observation was not controlled. There were times in the course of this patient's illness when the pain disappeared spontaneously. Such spontaneous improvement raises doubt as to the value of x-ray therapy.

5. Steegman, A. T.: Syndrome of the Anterior Spinal Artery, Neurology **2**:15-35, 1952.

Fig. 9 (Case 2).—The cavity of the syrinx and a typical gliotic reaction are seen on the left; the cord parenchyma, on the right. Notice the large number of thick-walled blood vessels. Hematoxylin and eosin technique; × 84.

The preservation of position sense and loss of vibration sense in both upper and lower extremities is noteworthy. This observation was made on many occasions and by many examiners. Alteration of position sense did not occur until late in the course of the illness. This type of sensory dissociation will be considered in the discussion. The preservation of sensation in the buccal and nasal mucosa, despite loss of similar sensibility on the face, is also of interest and represents another peculiar dissociation.

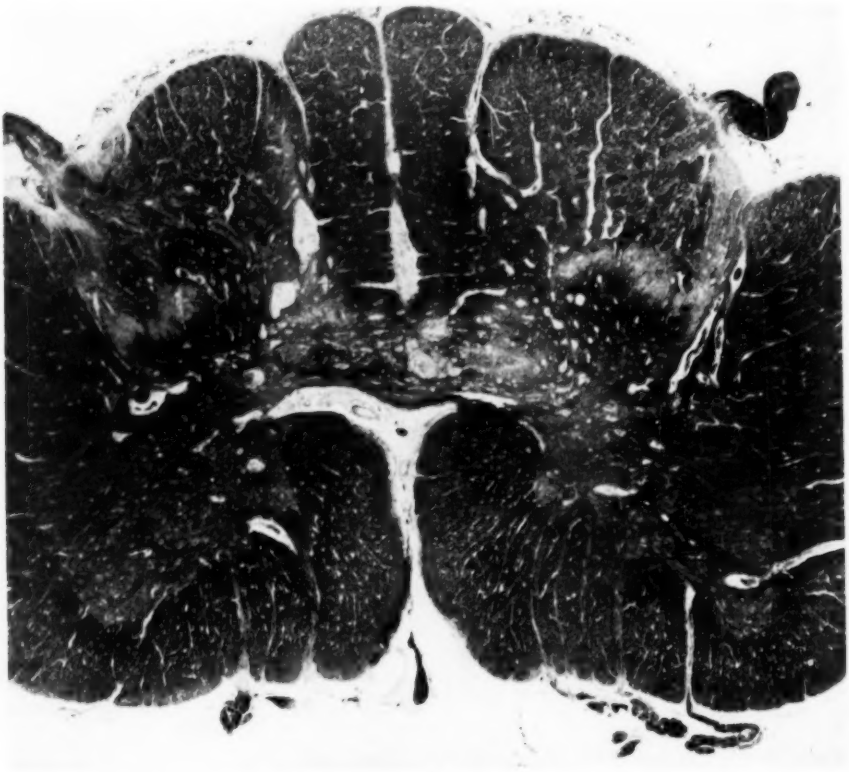

Fig. 10 (Case 2).—Gliosis without cavitation is present in the lower cervical region in the commissural region. Many blood vessels, some of them extremely large, are seen in the gliotic zone. Weil technique; × 18.

The pathologic findings are interpreted as an intramedullary vascular malformation, which resulted in destruction of tissue. There was a mild reactive gliosis and fibrosis limited to the areas containing such altered blood vessels.

Two cases remarkably similar in both clinical and pathologic details have been reported by Taylor, Greenfield, and Martin.[6] In both cases the authors commented on the large number and size of the vessels in and around the affected parts. A

6. Taylor, J.; Greenfield, J. G., and Martin, J. P.: Two Cases of Syringomyelia and Syringobulbia Observed Clinically over Many Years and Examined Pathologically, Brain **45**:323-356, 1922.

diagnosis of syringomyelia was made, and the hypothesis of venous stasis leading to syringomyelia was offered. They did not carry the interpretation further to include the concept of a vascular anomaly.

Case 2.—L. L., a clerk aged 54, gave a history of polyuria and occasional incontinence since he was a schoolboy. He always had been awkward and weak. There had been difficulty in adjustment to his surroundings since early childhood. At the age of 51, he had an attack of dizziness with falling, but was not unconscious. During the next three years, there were about a dozen of these attacks, and he finally entered Montefiore Hospital in 1929.

Examination revealed a man with a large brachycephalic skull. His mentality was that of a low-grade moron. The gait was spastic, with short steps, and a dorsal scoliosis was present. Motor power was reduced in the lower extremities but good in the upper extremities. The deep reflexes were generally hyperactive and equal on the two sides. There was no Babinski sign. The cranial nerves were normal except for irregular, unequal pupils, the right being smaller than the left. Sensation was intact.

Roentgen examination revealed a considerable increase in the capacity of the skull, and the shape was roughly quadrilateral. The sella turcica was larger than normal, and the posterior clinoid processes were partially destroyed. The existence of an intracranial neoplasm was suspected, but roentgenograms taken a year later were similar, and the final interpretation was that of long-standing internal hydrocephalus. The cerebrospinal fluid was under normal pressure and contained 3 lymphocytes per cubic millimeter, and the Wassermann reaction was negative.

The patient received only custodial care. In 1930 additional mental alterations were noted. He began to behave peculiarly and took to cursing his attendants loudly. Sacral decubitus, fever, and death occurred in rapid succession.

Necropsy was limited to the spinal cord. Macroscopic examination revealed a central cavity in the cervical region down to the fifth cervical segment and absence of cavitation below this. The remainder of the spinal cord had a normal appearance.

Microscopic examination revealed that a single cavity traversed the posterior commissure and extended for a short distance into the anterior and posterior horns. Laterally the syrinx was lined by proliferated astrocytes, arranged in orderly fashion and without mitoses. The inner lining of the cavity was a wavy band of collagenous connective tissue, in which there were a moderate number of endothelial cells. Within the cavity were a few unusually large blood vessels with thick connective tissue walls. Some had multiple lumens, suggesting recanalization. The cavity was independent of the central canal, the latter consisting of proliferated ependymal cells without an obvious lumen. There were unusually large and thick-walled blood vessels posteriorly and laterally at short distances from the cavity. The lateral and posterior funiculi, as well as the comissural fibers, were intact.

At another level of the upper cervical region a similar picture prevailed (Fig. 7). An additional feature was the prominence of medium-sized blood vessels in the connective tissue wall of the syrinx. Two large anomalous vessels lay in the cavity (Fig. 8). They had connections only dorsally, but not ventrally, with the sulcal arteries. Moderate numbers of small but thick-walled blood vessels lay in clusters in and around both the cavity and the glial proliferative reaction (Fig. 9). In the lower part of the cervical region the process was simply that of gliosis containing larger numbers of blood vessels than usual, but without cavitation (Fig. 10). There was neither descending nor ascending demyelination. The thoracic and lumbar segments were all anatomically intact. The central canal at these levels was composed of proliferated ependyma without a lumen.

Comment.—Unfortunately, the brain was not available for examination in this case. It is probable that most of the neurologic difficulties of this patient were related to a cerebral diplegia. There were never any sensory alterations, despite the moderately large size of the syrinx in the cervical region, and the motor signs were predominantly in the legs. This case illustrates an asymptomatic syringomyelic process. The spinal cord was expanded without significant alteration of gray or

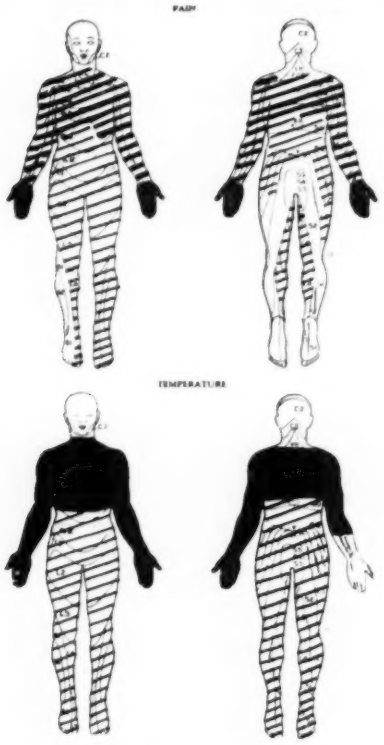

Fig. 11 (Case 3).—Alteration of pain and temperature sensation, January, 1934. Temperature sensation was more affected than pain sense, and cold sensation, more than heat sense.

Fig. 12 (Case 3).—The cavity occupies gray matter for the most part, with extensions into the white matter of the lateral columns. In the lower segments the posterior horn alone is affected. The posterior columns, though distorted, are anatomically intact. Weil technique; × 3.5.

white matter. The cavity with connective tissue lining and large numbers of malformed blood vessels was an instance of syringomyelia associated with vascular malformation, similar to that in Case 1. It is noteworthy that the patient did not receive radiotherapy; hence the vascular alterations cannot be the result of such treatment. The similarity of the vascular anomalies in this case and in Case 1 is striking. In both cases some of the blood vessels were too large, too mature, and their number too great to be explained as a simple reactive process.

Case 3.—S. M., a man aged 31, in 1910 noticed cramps in all his fingers, associated with "joint pains" in the hands. His fingers would slowly curl up, and he was unable to keep them straight. There were some paresthesias, the exact nature not being described. He slowly lost sense of temperature and ability to move his fingers. The condition progressed slowly. In 1924 he burned his left forefinger without realizing it. An infection developed, and the finger was amputated. From 1924 to 1930 his condition was unchanged. Subjectively, he did not lose sensation entirely and stated that he was able to perceive touch and extremes of heat and cold in the upper extremities. In 1930 he noticed atrophy of the muscles of the hands and arms. In the latter part of 1930 he complained of constipation and indigestion. Examination of sputum by his local physician revealed acid-fast organisms. He became weaker and dyspneic and lost about 10 lb. (4.5 kg.) in weight. He was admitted to Montefiore Hospital in 1934.

Examination revealed an emaciated, chronically ill, but cooperative and oriented patient with a mild right dorsal scoliosis. There was dullness to percussion over the upper half of both lungs. The right eyelid drooped. The right pupil was smaller than the left, but both pupils reacted to light and in convergence. The extraocular movements were full, and nystagmus was not present. Atrophy and fasciculations were present in the muscles of both upper extremities, being most striking distally. The hands were clawed, cold, and cyanotic, with dry, inelastic skin and an amputated left forefinger. The deep reflexes were absent in the upper extremities, and there was hyperreflexia in the lower extremities. The abdominal skin reflexes were not obtained. The Babinski sign was equivocal on the right. Temperature sensation (cold more than heat) was diminished over both arms and the chest, but there was mild impairment of sensation throughout the body below this level (Fig. 11). A similar distribution of impairment of pain sensation was present except that the involvement was more striking in the hands. Touch sensation was normal. Vibration sense was diminished in the hands, but position sense everywhere was normal.

Lumbar puncture failed to reveal evidence of block by manometric study. The total protein was 26 mg. per 100 cc., and there were no cells in the spinal fluid. The colloidal gold curve was normal. Roentgenograms of the chest showed extensive fibrotic tuberculosis of the upper lobe bilaterally. The major problem was management of pulmonary, and later laryngeal, tuberculosis. In February, 1935, the patient was discharged from the hospital. It was considered that both the syringomyelic and the tuberculous process were stationary.

The only additional information obtained was that he entered another hospital in March, 1936, and died there in May of the same year. Death was related to the progression of pulmonary tuberculosis. As far as can be learned, the neurologic findings were similar to those obtained at this hospital. The neurologic disorder lasted 26 years.

At necropsy only the spinal cord was obtained for study at Montefiore Hospital. From the cervical through the lumbar region, the spinal cord was thinner than usual. Throughout the cervical and thoracic regions a central cavity replaced practically all the gray matter, leaving only a thin shell of white matter on the anterior and posterior surfaces. The cavity was not seen macroscopically in the lower thoracic region.

Microscopic examination revealed that the cavitation decreased in size progressively from above downward (Fig. 12). The syrinx involved principally the gray matter and extended across the commissure. The posterior columns were well preserved, but there was demyelination in the medial portion of the lateral columns. In the thoracic region the cavity extended into both posterior horns and laterally, with demyelination of the medial part of the lateral columns. In the lumbar region the cavity was present in only one posterior horn.

Nissl preparations of the cervical region revealed an intact central canal. The cavity lay just posterior to the canal. An ependymal lining was present for a short distance just lateral to the central canal and consisted of about a dozen ependymal cells. Elsewhere the cavity was surrounded by an acellular rim, and this, in turn, by a zone of mild astrocytosis. Moderate numbers of thick-walled, small blood vessels were present, as well as one completely thrombosed vessel. At lower levels there was a similar picture. In the thoracic region the syrinx included the central canal. At some levels short stretches of ependyma covered portions of the cavity. In the lower thoracic and lumbar regions the central canal was again unaffected (Fig. 13).

Comment.—The onset of the disorder was with motor signs and pain. Objective sensory alterations occurred later. There was a long period in which the condition of the patient remained static. Pulmonary tuberculosis, and not the neurologic disorder, was responsible for the death of the patient.

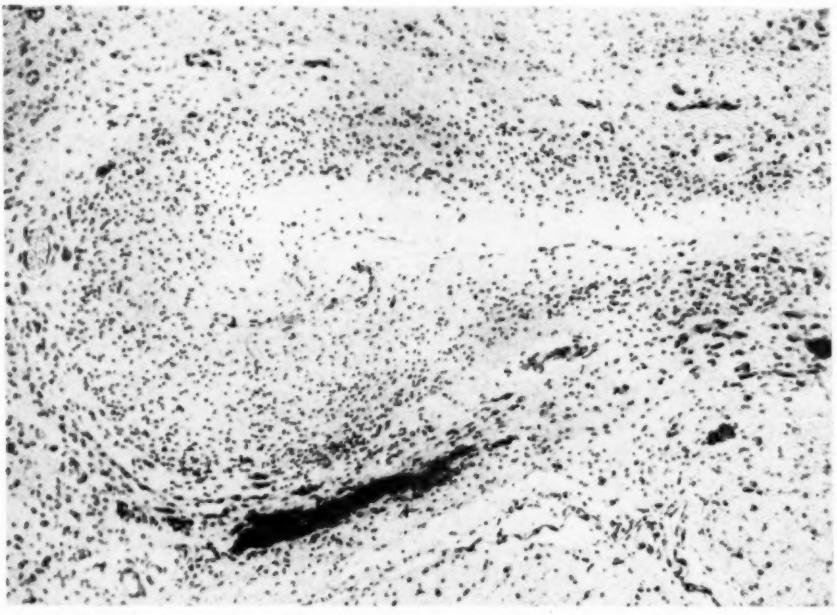

Fig. 13 (Case 3).—The proliferated central canal lies below and is without a lumen. It is independent of the cavity, which has a typical acellular rim and a mild gliosis surrounding it. Nissl technique; × 15.

Dissociation of vibratory and position sense was noted only in the hands, the site of lower motor neuron weakness. The intactness of the posterior columns is correlated with preservation of position sense. The loss of vibratory sensibility may be related to destruction of the medial portion of the lateral column. It is suggested that fibers subserving vibratory sense lie in the lateral columns adjacent to the anterior horns, rather than in the posterior columns (see "Comment").

It is striking that the cavitation involved gray matter almost exclusively, except for a minute amount of white matter in the ventral commissure and some extension of cavitation into the lateral funiculus. The cavity changed position in relation to the central canal, impinging on the latter in the midthoracic region but being separate in the cervical and lumbar regions.

Case 4.—A. H., a 47-year-old housewife, noticed in 1932 that she tired easily when walking and thus became aware of weakness in the lower extremities. A few months later, the toes of the right foot began to scrape the ground, and she had pain in the right knee on motion, but not spontaneously. In 1933 she noticed weakness of the right upper extremity, especially the hand.

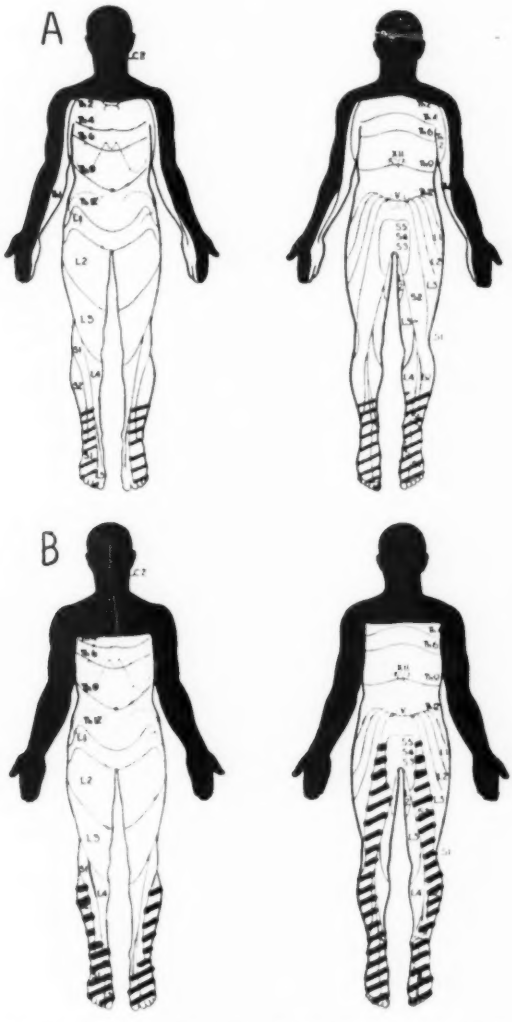

Fig. 14 (Case 4).—*A*, alteration of pain and temperature sensation in June, 1936. Heat sensation was more affected than cold sensation, and these were more affected than pain sense. *B*, sensory loss in June, 1945. The zone of analgesia and thermanesthesia has descended to include the upper three thoracic dermatomes. In addition, there is a mild diminution in the fifth lumbar-second sacral dermatome distribution. Pain and temperature sensations are now equally affected.

A few months later she had aching pains in the right shoulder, which were aggravated with movement of the joint. The pain then spread distally to involve the entire right upper extremity. The pain always was made worse by motion at any joint, but the joints were not swollen. Some-

time in 1934 the left hand became weak, and six months later she had mild pains in the left hand. The weakness of the extremities slowly grew worse, with greater involvement of the right side. In 1935 she noticed mild flexion of the fingers of the right hand and inability to extend these fingers completely. About this time she occasionally burned her fingers while cooking. There was no immediate awareness, but she experienced pains at the site of the burn when blisters appeared. She was still able to get about with support until April, 1936, when she had a sudden sharp pain in the lower part of the chest with fever. This was diagnosed as pleurisy, and she was confined to bed for four weeks. During the last week of this febrile illness, she became incontinent of urine and feces, and quadriparesis became more striking. She entered a hospital in May, 1936, where weakness of the larynx without weakness of the palate was noted and the diagnosis of syringomyelia was made on this basis. A lumbar puncture revealed a pressure of 110 mm. of water and yellow, clear cerebrospinal fluid. There was no evidence of block on manometric study. A second lumbar puncture revealed a colorless fluid; there is no report of the other findings. The blood serologic test for syphilis was negative. The patient was then transferred to Montefiore Hospital.

Examination revealed an obese woman, who appeared several years older than the stated age and who was perspiring profusely over the face. There were sacral decubiti. Mentally the patient was considerably retarded, answering questions slowly and exhibiting some impairment of recent memory, as well as poor ability to calculate. The patient, however, was illiterate, and orientation in all spheres was good. The right arm and both lower extremities were almost completely paralyzed except for some motion of the toes, and the left upper extremity was moderately weak. Tonus was increased in the lower extremities. The intrinsic muscles of both hands were atrophied. There were occasional fasciculations in these wasted muscles and in both biceps. The biceps reflex was absent on the right and was just perceptible on the left. The triceps reflex was normal on the right and hyperactive on the left. The deep reflexes in the lower extremities were hyperactive and equal on the two sides. There were a bilateral Babinski sign and absence of abdominal skin reflexes. Examination of the cranial nerves revealed poor reaction of the pupils to light and in convergence, paralysis of the left external rectus, absence of the corneal reflexes, and slight weakness of the right half of the palate. The voice was high-pitched and hoarse. Sensory examination revealed that touch sensation was preserved, but there was loss of pain and temperature sensation over the face, neck, and outer aspects of both arms (Fig. 14 *A*). The diminution was best demonstrated with heat, less well with cold, and least with painful stimuli. A minimal alteration was noted in the feet. There was slight impairment of position sense in the toes on the right, but vibratory sensation was absent over the entire body, being present only on the face. Urinary and fecal incontinence were present, with decreased tone of the rectal sphincter.

Lumbar puncture revealed clear and colorless fluid, which contained 8 lymphocytes per cubic millimeter, 31 mg. of protein per 100 cc., and a negative Wassermann reaction. There was a fairly marked productive spondylitis in the lower cervical vertebrae.

The diagnosis of syringomyelia was made, and x-ray therapy was given over the bulb and cervical portion of the cord in doses of 200 r four times a week in a total dose of 3,600 r. It was thought that improvement was obtained after this. This impression was based on the finding that there was "some slight recovery of function in the right arm."

During 1937 and 1938 there was very little progression except for a slow increase in weakness. In 1939, there was abdominal distention, and a mass in the left lower quadrant was palpated. Roentgenograms of the gastrointestinal tract failed to reveal abnormalities. In 1940 there were complaints of severe burning sensations, starting at the waist and spreading up over the body and face. These occurred at intervals of about an hour. Examination revealed coarse nystagmus on left lateral gaze and rotator nystagmus of the right eye on right lateral gaze. The speech was slow and nasal. Quadriparesis was present, with only slight movement of the upper extremities. All limbs were spastic, and the hands had flexion contractures. The zone of loss of pain and temperature sensation included the face and head down to the first thoracic dermatome, but touch sensation was still preserved. Cystometric studies done at the beginning of 1940 revealed a hypertonic urinary bladder, but in October of the same year the bladder was hypotonic and there was a change from incontinence to inability to void. By 1941 there were complete paralysis of the upper extremities, diminished position sense in the toes and fingers, and absence of vibra-

tory sensation. She constantly complained of severe pain in all extremities. In December, 1941, pain in the right eye, with high intraocular tension, was treated by iridectomy, followed, because of failure to relieve pain, by an enucleation. Examination of the eye revealed a malignant melanoma of the choroid with secondary glaucoma. A corneal ulcer appeared on the left eye and thereafter healed. From 1942 on, there were intermittent complaints of pain in the hands and heels. In 1944 the sensory level, in which heat sensation was most affected, was at the third thoracic dermatome. Incontinence had then returned. In 1945 a second band of sensory dissociation was found in the distribution of the fifth lumbar to the second sacral dermatome (Fig. 14 *B*). This was interpreted as indicating the presence of two cavities, one in the cervical portion of the spinal cord and the other in the lumbosacral region. In 1945 and 1946 she sustained fractures of the femurs as a result of minimal handling. Recurrent infections of the genitourinary and respiratory tracts occurred. In 1947 a trial of Dibenamine was given for the facial sweating, with definite inhibition. Toward the end of July, 1947, fever, enlargement of the liver, and pitting edema were noted. She died in August, 1947, the disorder having lasted 15 years.

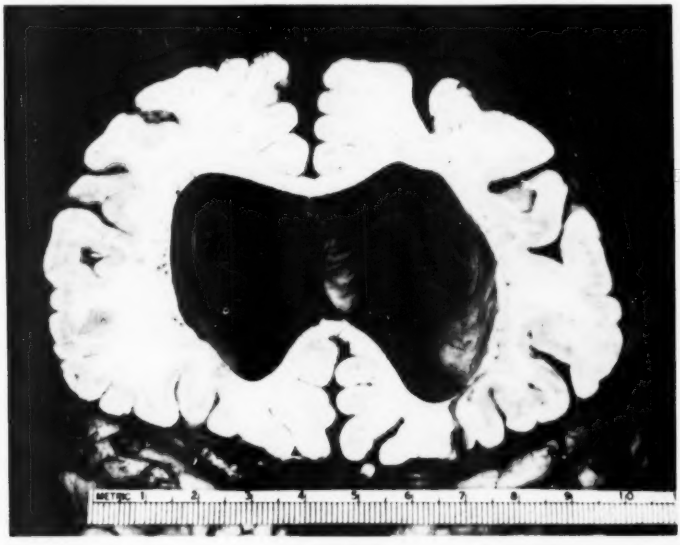

Fig. 15 (Case 4).—Enormous dilatation of the lateral ventricles is shown in the frontal region. Note that the cortical gray matter is of average width and is not altered. The dilatation is entirely at the expense of white matter.

Necropsy revealed the operative absence of the right eye and metastases of malignant melanoma to the liver, with extensive hemorrhage and necrosis in the latter. There was chronic cystitis, and the left kidney contained numerous calculi in the pelvis, as well as pyelitis and moderate hydronephrosis. There were focal pneumonia, congestion, and edema of the lungs. A nodular colloid goiter was present.

The floor of the third ventricle of the brain bulged in cystic fashion, compressing and flattening the optic chiasm and tracts. The posterior wall of the third ventricle was thin and bulged posteriorly above the pineal body and the corpora quadrigemina. There was a large cerebellar pressure cone. Adhesions were not found between the cerebellar lobes and the medulla. The ventricular system was enormously dilated, with the septum pellucidum remaining as mere shreds between the lateral ventricles (Fig. 15). The interventricular foramens were huge. The ventricular dilatation was at the expense of the centrum ovale, and the cortical gray matter was not unusually narrow. The third ventricle and the aqueduct of Sylvius in its anterior portion were dilated, but the remainder of the aqueduct and the fourth ventricle were normal in size.

The junction of the medulla and cervical cord showed evidence of syringomyelia. The entire spinal cord had a boggy, cystic appearance and was increased greatly in the transverse diameter and correspondingly decreased in the anteroposterior diameter (Fig. 16). In the cervical region the greatest anteroposterior diameter was 4 mm. The central cavity was surrounded by a thin rim of white matter. The cavity decreased in size, and the volume of intact parenchyma increased gradually as the lumbar region was approached. There was only a thin slit traversing the commissure and the posterior part of the anterior horns in the lumbar region. In the sacral region there were two separate cavities in the gray matter (Fig. 16). The coccygeal region was intact.

Microscopic examination revealed that most of the ependymal lining of the lateral ventricles was absent. There were scattered foci of normal ependyma lining the ventricular system. The subependymal cell plate, whether denuded or lined by ependyma, was not excessively gliotic

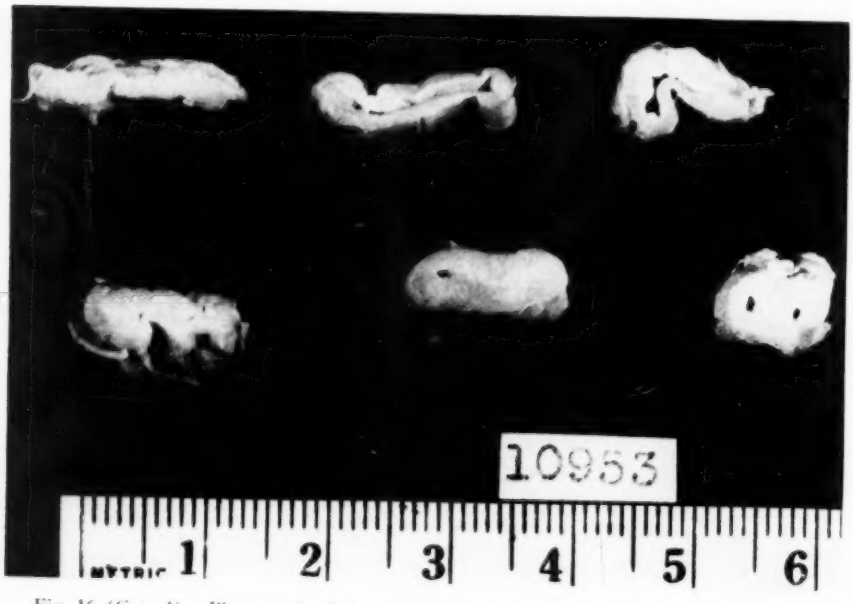

Fig. 16 (Case 4).—Photograph of the spinal cord showing the collapsed large cavity in the cervicothoracic region and two separate cavities in the posterior horns of the lumbosacral region.

but had the usual appearance. There were no histologic abnormalities to account for the hydrocephalus. The only alteration noted in the cerebrum was a condensation of oligodendroglia for a short distance around the ventricular system. The cortical gray matter had a normal histologic appearance. The fourth ventricle at the midportion of the pons was normal both in size and in the appearance of the ependymal lining. In the lower part of the medulla there were mild gliosis and minimal cavitation in and around the floor of the 4th ventricle.

The cervical portion of the spinal cord contained a large cavity, which was in the transverse plane (Fig. 17). The cavity extended into both anterior horns and partly into one posterior horn. Demyelination was present in both lateral funiculi, but predominantly in the dorsal portions. The dorsal columns, although shrunken and distorted, were only partially demyelinated. The large cavity was partially lined by ependyma, even in places at a relatively great distance from the central canal. Other portions were lined by a minimal gliosis, or by normal tissue, appearing simply as a cavity without reaction. Small islands of parenchyma protruded into the cavity in a few places, and a few thick-walled blood vessels lay within the orifice. In the

lumbar and sacral regions there were two cavities in the gray matter on either side of the central canal. The latter was not implicated. Minimal slits in the gray matter were seen in the coccygeal region.

Comment.—This case in many ways is a typical instance of syringomyelia. The onset of symptoms was with weakness, pain, and then burning of the skin without awareness. Pain in anesthetic zones was severe later in the course of the disease. This "central pain" always has been difficult to understand because it occurs in areas in which the known pain fibers have been destroyed.

Sphincteric incontinence is not common in this disease, even with bilateral pyramidal tract involvement, but in this case may be explained by the implication of the sacral segments of the spinal cord. Cervical spondylitis was noted four years after the onset of the disorder. Such arthropathy may develop within three weeks,[7] but usually takes some years. It is of interest that the correct diagnosis was established on the basis of laryngoplegia without palatoplegia.

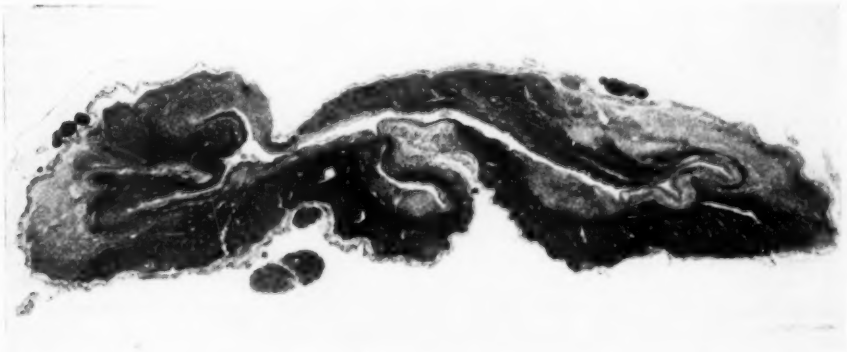

Fig. 17 (Case 4).—The spinal cord is collapsed. The cavity is mostly in gray matter. Demyelination is extensive and severe in the lateral columns. Weil technique; × 11.

Repeated observations indicated that there was loss of vibratory sensation with fairly good preservation of position sense. Only after many years was there definite diminution of position sense, but this loss never became complete. This picture is correlated with the severe destruction of lateral column fibers and relative preservation of the posterior columns.

Although x-ray therapy was considered to be of value on one occasion, it should be noted that the improvement was a subjective observation on the part of one examiner. Despite this supposed improvement, the patient slowly became worse. The course in this patient was not different than that in untreated patients with syringomyelia.

The clinical diagnosis of two separate cavities on the basis of the sensory findings was not confirmed. Actually, a single cavity extended down through the cervical and thoracic portions of the spinal cord, diminishing in size at the lower levels and becoming bifid in the lumbar region. It is clear that cavitation in the spinal cord

7. Pendergrass, E.; Gammon, G. D., and Powell, J. H.: Rapid Development of Bone Changes in a Patient with Syringomyelia as Observed Roentgenologically, Radiology **45**:138-146, 1945.

may be without clinical symptoms, either in whole (Case 2) or in part. The course was complicated by extension of a malignant melanoma, and death was related to metastases of this tumor, rather than to the neurologic disorder.

A large hydrocephalus may be associated with syringomyelia. The significance of the hydrocephalus is not clear because its cause is not known. Pathologically, the usual fibrous or glial reaction around the lining of the dilated lateral ventricles is lacking. Syrinx formation almost never occurs above the pons. It seems therefore that hydrocephalus is an associated process, and not the same condition as that encountered in the spinal cord.

Case 5.—F. L., a 17-year-old girl, experienced slight stiffness of the right side of the neck in 1929. Two years later paresthesias in the right occiput were noted and were felt thereafter at irregular intervals. The patient had her first pregnancy in 1932, at the age of 20. Six months afterward, at the beginning of 1933, it was pointed out to her that she was shuffling her right leg. At the time this was called to her attention, she herself noticed clumsiness and weakness of her right hand. The weakness of the right side progressed slowly from the hand upward and in the lower extremity from the foot upward. Over the years there was increasing difficulty in walking. In 1935 she had sensations of fatigue or of drunkenness when she stayed awake late. Occasionally she felt as if she were "dead from the hips down." In March, 1936, an attack occurred, lasting 30 minutes, in which she had a steady hammering in her head, blurred vision, and a feeling of nausea.

In November, 1936, she was admitted to a hospital. Lumbar scoliosis was noted. There were slight weakness in the right upper and lower extremities and some atrophy. The right arm was ataxic. The deep reflexes were increased generally, but more so on the right side. The Babinski sign was present on the right and was equivocal on the left. The right pupil was smaller than the left. There were fasciculations of the tongue with atrophy of both lateral borders. There was questionable diminution of vibratory sense in the right leg; other modalities were not described. Mentally she was said to show emotional overflow and overproductivity.

The protein content of the cerebrospinal fluid was 12 mg. per 100 cc. There were no cells in the fluid, and the Wassermann reaction was negative. Roentgenograms of the skull, chest, and cervical vertebrae were normal. The red blood cell count was 3,600,000 per cubic millimeters, interpreted as indicating a secondary type of anemia. The diagnosis of syringomyelia of the upper part of the cervical cord was made, and she received a course of x-ray therapy, the amount of radiation being unknown. Thereafter she had frequency and urgency in urination, without incontinence. In 1937 she was seen at another hospital, where the diagnosis of multiple sclerosis was made on the basis of bilateral pyramidal tract signs, impairment of vibratory sensibility in the right hand and foot, weakness, and nystagmus. In 1939 the left hand and leg became weak and stiff; then the shoulders and the lower part of the neck became "tired." In May, 1939, a therapeutic abortion was performed because of the diagnosis of syringomyelia. She then received 2,700 r of x-radiation to the upper cervical and thoracic regions.

On admission to Montefiore Hospital in July, the blood pressure was 98/64. Examination showed a well-developed woman who leaned to the left and had a forward tilt of the left shoulder. The right arm and leg were paretic. The right hand was held in extension with the fingers flexed. The right lower extremity was stiff, and there was a minimal degree of weakness in the left lower extremity. She walked with circumduction of the right leg. The deep reflexes were hyperactive. The Babinski sign was present on the right and equivocal on the left. The left pupil was larger than the right. There was nystagmus on right lateral gaze. The tongue was atrophic and had fasciculations. There was loss of vibratory sensation from the shoulder blades down, but position sense was intact. Pain sensation was diminished in the second to the fourth cervical dermatomes, and there was a mild diminution on the right side of the face (Fig. 18 *A*). Cold sensation was diminished in the same distribution as pain sense. Touch and heat sensations were intact.

Roentgenograms of the spine revealed moderate spondylitis involving the bodies of the fourth, fifth, and sixth cervical vertebrae. The cerebrospinal fluid protein was 18 mg. per 100 cc. There was a negative serologic reaction for syphilis and absence of block on manometric study. Blood

sugar and blood urea nitrogen were within normal limits. The red blood cell count was 3,700,000 per cubic millimeter. She was discharged from this hospital in September, 1940, after receiving 1,200 r to each of three cervical portals, but continued to show progression of the disease, with increasing weakness of the left side, which by 1942 had become almost complete paralysis. She was admitted to another hospital in November, 1942. Temperature, as well as pain, sensation was then altered in the upper cervical dermatomes. A laminectomy of the first, second, and third cervical vertebrae revealed "a swollen cord with considerable softening." The cord was incised longitudinally through the middle part of the posterior column, and a considerable amount of

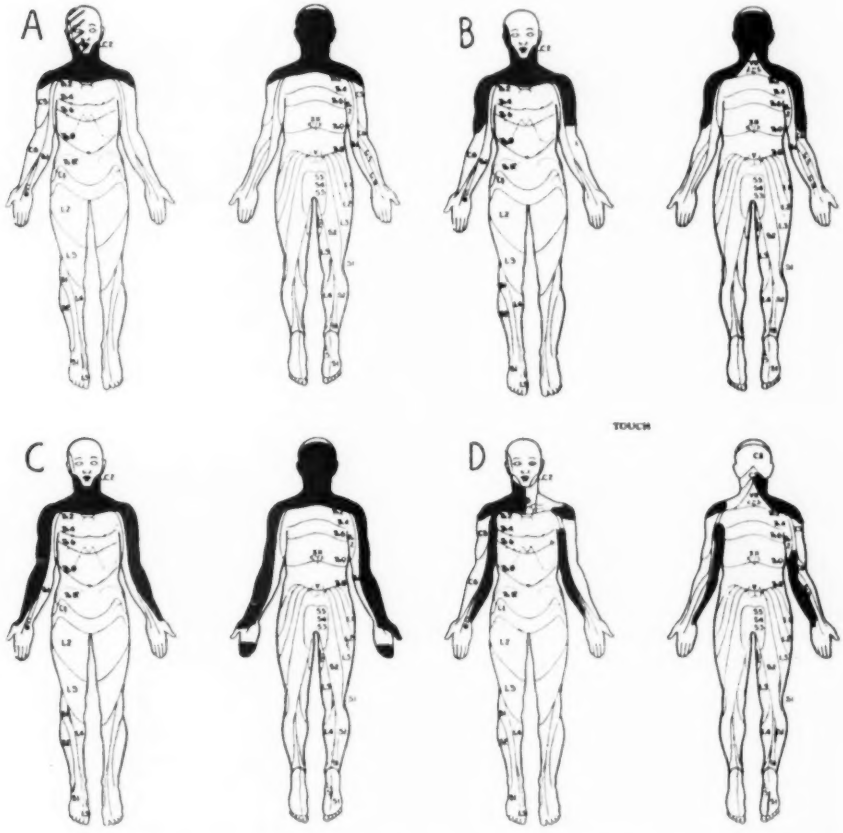

Fig. 18 (Case 5).—*A*, alteration of pain and temperature sensation in July, 1940. The disturbance involved cold and pain sensation. Heat sensation was normal at this time, as was touch sensation.

B, sensory alteration in January, 1942. Pain and temperature sensation are now equally affected. The level has descended to include the fifth cervical dermatome. The mild involvement of the right side of the face found in 1940 was not noted in 1942.

C, sensory alteration in May, 1946. The level has descended further, to the fifth cervical dermatome and the backs of the fingers.

D, sensory alteration in May, 1946. Touch sensation has now become affected.

fluid was evacuated. A fistulous connection between the cavity and the subarachnoid space was established by cutting the dentate ligaments and suturing them to the lining of the cavity. She was then readmitted to Montefiore Hospital in December, 1942. On this admission she was

confined to bed, with paralysis of all extremities. The Babinski sign was present bilaterally. There was weakness of the right sternocleidomastoid muscle, and the tongue was atrophic. The level of loss of pain sensation was down to the fifth cervical dermatome (Fig. 18*B*). Position sense was lost in the right upper and lower extremities, and vibration sense continued to be absent. It was thought that the three courses of x-ray therapy and the establishment of a fistula were all without effect. The patient stated that her symptoms were always accelerated after x-ray therapy. She continued to grow worse and, because of this, was given 2,000 r to each of two portals in the neck. This was not followed by any noticeable change immediately, but she slowly became worse throughout 1945. The uvula was found to deviate to the left, and the left masseter muscle became weak. Wasting of the muscles in all extremities continued. It became difficult to swallow solid food. In 1946 the pain and temperature level was down to the seventh cervical dermatome (Fig. 18*C*), and touch sensation was then affected (Fig. 18*D*). Position sense was altered in all four extremities. Difficulty in swallowing and breathing continued and increased through 1947. In 1948 she was able to move slightly only the left lower extremity. The right upper extremity was flaccid. Plantar stimulation resulted in flexor spasms. Despite her prolonged invalidism, her mental outlook and disposition remained surprisingly good. In October, 1948, she complained of burning sensations in the hands, and intermittent pains in all four extremities continued to occur. In late 1949 there were numbness and tingling in the face. She became increasingly dyspneic and cyanotic and in January, 1950, died in respiratory failure. The duration of the disorder was 20 years when the stiffness of the neck is considered as the first symptom. The duration was 16 years from the first evidence of weakness.

Necropsy revealed mucopurulent plugs in the bronchial tree, atelectasis, and focal pneumonia.

The cerebral hemispheres were symmetrically and well developed. The left vertebral artery was incorporated in a dense, opaque leptomeninx. The arachnoid over the medulla and over both foramens of Luschka was thick, and the medulla itself was firmly adherent to the cerebellum by the thick arachnoid.

The cut surface of the brain was wet, and the gray matter stood out prominently but was of normal thickness. The ventricles were not dilated, and the cerebral hemispheres appeared normal. The aqueduct of Sylvius was of normal size, as was the fourth ventricle. At the level of the inferior olives there was a slight brown discoloration of the right and left reticular formations with extension into the olives. Both pyramids were small and had a chalky appearance.

In the spinal cord the dura was normal except in the upper cervical region, where it was fibrotic and thick at the old operative site. The fistula created by the neurosurgeon was not visible. The spinal cord was flattened dorsoventrally and was crepitant. Throughout the cervical and thoracic region the central portion was replaced by a cavity, which diminished in size from above downward (Fig. 19). The remaining rim of spinal cord tissue had a chalky and translucent appearance. In the lower lumbar and upper sacral segments there was only a small central defect, 2 mm. in diameter.

Microscopic examination revealed that the cerebral hemispheres and the aqueduct of Sylvius were lined by intact ependyma. There was no cavitation in the mesencephalon. The fourth ventricle in the midpons was minimally enlarged, and its lateral projection was larger on one side. There was, however, no unusual periventricular gliosis. The basilar portion of the pons contained a minute slit, which traversed the pontine nuclei and was rimmed by clusters of glial cells. At the level of the transition of pons and medulla the fourth ventricle was moderately dilated. The ependymal lining for the most part was intact, and dorsally there was mild ependymal proliferation with minimal gliosis. Ventral to both olives there were irregular cavities lined in part by large blood vessels and in greater part by a glial cell proliferation. These impinged partially on the pyramids but not on the olives.

The medulla at the level of the olives revealed a malformation of the floor of the fourth ventricle. An intact ependymal lining dipped deeply into the parenchyma in the midline. The cavities previously described lying between the olives and the pyramidal tract were also present. Lower in the medulla the midline dip of the floor of the fourth ventricle reached two-thirds of the distance to the ventral surface. The syringes resulted in a partial separation of the ventral tips of the two pyramids. In addition there was an anomalous distribution of cerebellar tissue, which descended to the ventral edge of the olive on both sides, as in the Arnold-Chiari malformation. At the upper cervical levels an enormous cavity replaced most of the substance of

the spinal cord. Much of the remaining, thin rim of myelinated fibers was demyelinated, but the spinal roots were intact. Slightly lower, in the uppermost cervical region, the cavity occupied a central position, but there were remnants of the anterior horns. The remaining myelin, for the most part, was intact except in the lateral funiculi. At this cervical level the cavity was lined by a homogeneous collection of astrocytes, lying in orderly fashion. Only a very short segment of the rim was lined by ependyma, and this was some distance away from the central canal. Many small blood vessels were seen peripheral to the gliotic rim.

In the lower cervical level many large and small blood vessels were present in the cavity. A long extent of ependymal lining was present. In the lumbar region, the cavity was in a central position, but an extension into the posterior median septum was filled with blood vessels. There was a fairly complete ependymal lining on the ventral portion of the cavity, and the central canal was not seen.

Comment.—The onset of illness in this patient was unusual if it is assumed that the stiffness of the neck and paresthesias in the right occiput were a part of the disease. The disorder remained unilateral with hemiplegia, for six years, although the ultimate outcome was the more usual bilateral involvement.

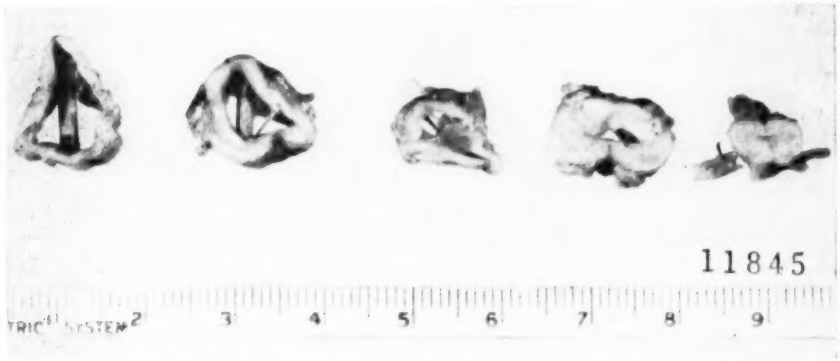

Fig. 19 (Case 5).—Photographs of the syrinx at different levels of the spinal cord. The collapsed walls of the two cervical segments have been spread by the insertion of match sticks. Only a thin shell of tissue remains at the upper level. The cavity grows progressively smaller in the lower segments.

The sensory alterations are of great interest in revealing the peculiarities of sensory dissociation which may occur in syringomyelia. In Case 4 heat and cold sensations were more affected than pain. In this case pain and cold sensations were more affected than heat. For a time heat sensation was actually intact when pain and cold sensation definitely were diminished.

The alteration of vibratory sensation and its dissociation from position sense are notable. Early in the course of the disease, in 1936, when there were right-sided motor signs, a questionable diminution of vibratory sense was noted in the right leg. Weakness of the right side and definite impairment of vibratory sense on this side were noted at another hospital in 1939 and, in part, led to the mistaken diagnosis of multiple sclerosis. Vibratory sense later was lost on the left side as motor signs appeared on this side. It was only in 1942 that position sense became altered and this affected first the right side of the body, but by 1946 both sides of the body were deficient in position sense. During this time vibratory sense was absent in all parts of the body except the head. The close relation of loss of vibration sense with motor signs rather than position sense is striking.

X-ray therapy unquestionably was without value in this case, as judged by the course. The patient thought she was made worse by such treatment. The surgical creation of a fistula was without value and was only temporary, the connection between cavity and subarachnoid space not being found at necropsy.

Clinicopathologic correlations partly were deficient, as in Case 4. A cavity in the cervical region, which was enormous, diminished in size progressively down through the sacral region, but there was no clinical evidence of cavitation in the thoracolumbosacral regions. This was in part related to the failure of the cavity to destroy the commissural fibers. Cavitation frequently may be asymptomatic (see also Case 2).

An interesting additional feature was the presence of an Arnold-Chiari malformation in association with syringomyelia. It is unlikely that this was the cause of the cavitation because the syrinx was seen as low as the sacral region. It is more probable in this case that these were associated disorders.

Case 6.—B. M., a 67-year-old housewife, was admitted to Montefiore Hospital in March, 1939, and died the same month. The history on admission was difficult to obtain because the patient was uninterested in answering questions. The following information was obtained from abstracts of other hospitalization records. She had been admitted to a hospital in 1925 complaining of pain behind the right ear, which began at the age of 41. Loss of power and of sensation in the lower extremities occurred at the age of 51. Examination revealed unequal pupils and right facial weakness of central type. A slight tremor was present in both hands. The deep reflexes in the lower extremities were hyperactive but equal, and there were no pathologic reflexes. Sensory findings were those of "the dissociated type of a syringomyelia," being more extensive up to the second cervical dermatome on the right side and up to the third cervical dermatome on the left. Vibratory and position sense were "little affected." A roentgenogram of the cervical spine was normal. Lumbar puncture was said to give negative results. Diathermy to the cervical region failed to result in benefit.

There are no known details of the history in the intervening years. In March, 1939, she was examined at another hospital, complaining of inability to move her arms above her head of a few years' duration. She also had complaints of constant pain in the back, difficulty in walking, spells of dizziness and fainting, pain over the right ear, sensation of a burning needle in the head on the left side, and numbness on the left side of the body.

Examination revealed an elderly woman with moderate obesity. She walked slowly on a wide basis and found it necessary to use her upper extremities for support. There were no atrophies, and muscle strength was fair. The deep reflexes were absent in the upper extremities, but were equal and active in the lower extremities. The Babinski sign was not elicited. There was loss of pain and temperature sensation over the left side of the body, but it was thought that the patient was not a good witness. Alterations in vibratory and position sense, if present, were not reported. The cerebrospinal fluid examination revealed a protein content of 34 mg. per 100 cc. and 2 cells per cubic millimeter. The Wassermann reaction was negative. The cervical spine appeared normal on roentgenographic study, as was the skull, except for evidence of vascular calcification in the latter.

The history obtained at Montefiore Hospital was rambling and irrelevant and added little except that she gave no history of having burned herself. Her intellect was low, and insight was lacking. A few days after admission the patient had an attack in which she became weak and sank to the floor, with an ashen color. The blood pressure could not be obtained. She continued in a state of shock and died. It was thought that she had a coronary artery occlusion.

Necropsy revealed generalized arteriosclerosis. The heart was hypertrophied and dilated, and a branch of the left coronary artery was completely occluded. An old thrombus was present in the right pulmonary artery.

Externally the brain showed striking atherosclerosis of the vessels at the base. The floor of the third ventricle protruded inferiorly. Section disclosed moderate dilatation of the entire ventricular system, without obstruction. The corpus callosum was thinner than usual. The aqueduct of Sylvius was also dilated, as was the fourth ventricle. The spinal cord was thinner than usual

in the cervical and thoracic segments. The upper cervical region contained a central cavity. The gray matter was largely destroyed, and the white matter formed a thin shell around the cavity. The syrinx diminished in size in the lower thoracic region, grew larger at the upper lumbar levels, and disappeared below this.

Microscopic examination revealed that the gray matter of the cerebrum was normal except for atherosclerosis of some blood vessels. The white matter was thin, but reactive gliosis was not present. The lateral ventricles and aqueduct of Sylvius were dilated and devoid of ependyma in large parts of their surfaces. The surrounding glial cell plate was not remarkable. The level representing the transition between medulla and spinal cord contained separate cavities, the larger one affecting the commissure and one posterior horn, the smaller one lying within the intermediate cell column. There was demyelination involving the comma tracts and the ventral part of the fibers surrounding the posterior median fissure. In addition, there was a mild degree of demyelination of the lateral columns. The cavities were independent of the central canal. The latter was minimally enlarged and surrounded by proliferated ependymal cells. There was

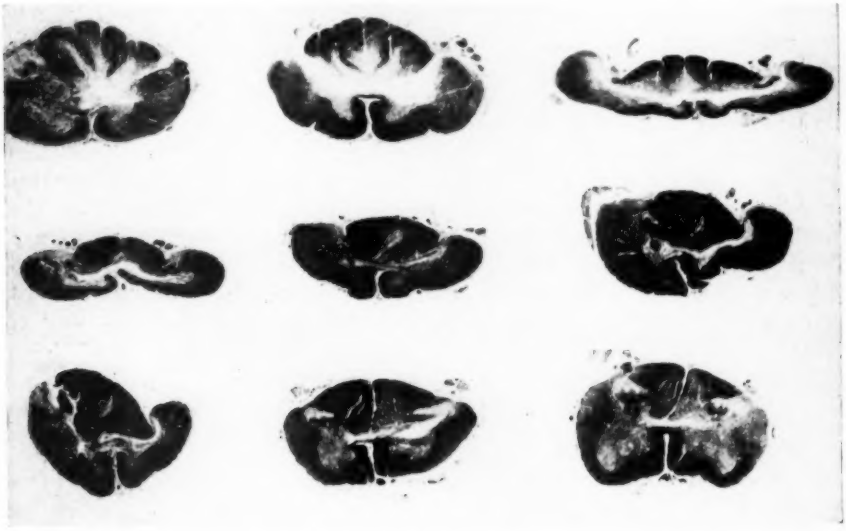

Fig. 20 (Case 6).—The largest cavity is in the cervical segments. Only one posterior horn is involved in the lower regions. Weil technique; × 3.75.

mild gliosis in the affected posterior horn. The lining of the cavities was composed of a small glial reaction. Within the larger cavity there were small islands of neural tissue.

A large single cavity was present at the midcervical level. It affected the gray matter and was continuous from one posterior horn through the dorsal commissure and into the other posterior horn (Fig. 20). The ventral commissure was not affected, and there was demyelination of the adjacent ventral part of the posterior columns. A minimal degree of lateral column involvement was also present. The cavity and the central canal were completely separated, and the syrinx was not lined by ependyma at any point. Gliosis at the edge of the cavity was minimal.

The largest cavity and the greatest amount of flattening were noted at the lower cervical level. Surrounding demyelination affected the ventral part of the posterior columns and the corticospinal tract, especially on one side. At this level the central canal was not seen. A long row of ependymal cells lined the central portion of the cavity, but the lateral portions were minimally gliotic, without ependymal lining. A few thick blood vessels lay at one edge. At the lowermost cervical segment the cavity was smaller and involved the commissural region

but extended into the ventral part of the posterior horns. A few unusually large blood vessels were present at the edge. These vessels had thick, fibrous, homogeneous walls. An ependymal lining was present in most of the ventral half of the cavity.

In the upper thoracic region the cavity extended from one column of Clarke through the posterior commissure and into the opposite posterior horn. The central canal was patent and surrounded by a few proliferated glial cells. The anterior horns, although not part of the cavity, contained many shrunken cells. In the midthoracic region the cavity was largely in one posterior horn. The upper lumbar level contained a cavity which was independent of the central canal and involved only one posterior horn. The central canal was lined by intact cuboidal epithelium but was surrounded by proliferated ependymal cells. There was no connection between the central canal and the cavity in the posterior horn.

In the lumbar enlargement only a minute cavity could be seen, surrounded by a moderate degree of glial-cell proliferation. The central canal contained only proliferated glial cells. Some anterior horn cells at this level were pale and others considerably shrunken in size.

Comments.—The history has obvious inadequacies, although it is apparent that syringomyelia was present when the patient was first hospitalized. The course was typically long, and was complicated by cerebral arteriosclerosis and probably by the development of a pronounced internal hydrocephalus. The peculiar mental state may be explained by the latter mechanisms.

Pathologically the case is typical. It demonstrates well the central cavity affecting the gray matter predominantly, with major involvement of the cervical region. Also well shown is the fact that the central canal may or may not be implicated and that ependymal cells may or may not participate in the process of syrinx formation. The existence of a vascular malformation is suggested at a few levels. The limitation of the process to one posterior horn in the lower parts of the spinal cord has been noted before but is worthy of comment. It casts doubt on the validity of the concept that syringomyelia is related to failure in midline fusion.

Case 7.—E. B., a 57-year-old housewife, was admitted to another hospital complaining of cough and loss of weight of six months' duration. The history relating to her neurologic disorder was limited to the statement that she had suffered numerous burns of all extremities and the trunk. Unfortunately, there were no details as to the symptoms or duration and progress of the disease. Examination revealed scoliosis and numerous scars of burns on the arms and shoulders. The middle finger of the left hand was deformed and contracted. There were small ulcers on the other fingers of this hand. Neurologic examination revealed that the pupils were equal and reacted to light and in convergence. The intrinsic muscles of the hand were atrophied bilaterally, and she was unable to flex her fingers. The lower extremities were spastic. The deep reflexes were absent in the upper extremities but hyperactive in the lower extremities. The Babinski sign was not present. Sensory examination was not considered reliable, particularly because the patient did not wish to be tested with painful stimuli. It was thought that pain sensation was decreased or absent from the lower cervical to the upper lumbar region. Vibration sense was absent up to the clavicle, but position sense was intact.

The Wassermann reaction of the blood was negative. There were moderate osteoarthritic changes in the lower thoracic and upper lumbar portions of the spine, as well as scoliosis. The problem of her respiratory difficulty was the main concern of the physicians. A decubitus appeared in the right sacral region eight days prior to death. The latter was associated with respiratory failure and interpreted as an asthmatic attack.

Necropsy revealed pulmonary emphysema and numerous caseocalcific tuberculous nodules in the apex of both lungs. Only the spinal portion of the neuraxis was available for examination. This was described macroscopically as being thinner than usual and containing a large cavity in the cervical, thoracic, and upper lumbar regions. Only three lower levels of the spinal cord were studied microscopically.

The spinal cord in the thoracic and upper lumbar regions was extremely shrunken. The cavity in the thoracic region included the dilated central canal but extended beyond this structure

into both lateral columns. The cavity was surrounded by a zone of demyelination, which reached farther into the lateral columns (Fig. 21 *A*). A thin band of demyelination was noted dorsally around the posterior median septum on either side of the fasciculus gracilis. The major part of the posterior columns was intact. The ependymal lining was a single layer of cuboidal epithelium on most of the dorsal aspect of the cavity. There was only a small segment of ependyma ventrally. The remainder of the cavity was lined not by ependyma but by moderate gliosis. A few small

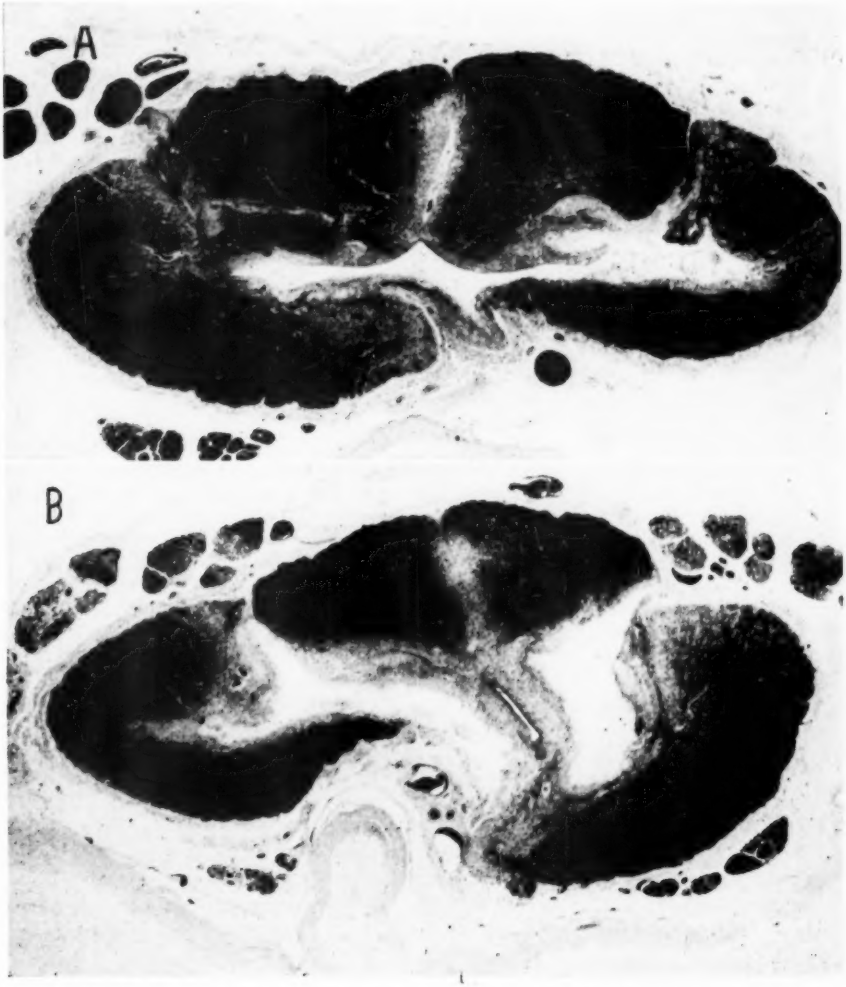

Fig. 21 (Case 7).—*A*, a single cavity in the gray matter includes the dilated central canal, as in hydromyelia; but there is rupture of the lateral edges to form syringes. Demyelination extends into the anterior and lateral funiculi and in the posterior column along the posterior median fissure. Weil technique; × 22.5.

B, the central canal is mildly dilated but is not involved in the process of cavitation. There are two separate cavities affecting the gray matter. Note the dilated blood vessels in the wall of the cavity on the left. The extension of demyelination around the cavity is similar to that seen in Figure 21*A*. Weil technique; × 25.

blood vessels with thick walls lay in the cavity and surrounding it. In the upper lumbar region there was an intact, but mildly dilated, central canal (Fig. 21 *B*). Two separate cavities occupied much of the gray matter, chiefly of the posterior horns. A rim of demyelination surrounded the cavities and, in addition, extended dorsally into a small portion of the fasciculus gracilis on either side of the posterior median septum. The surrounding zone of demyelination was irregular and in a few places extended out to the periphery.

At this level the central canal was composed of a single layer of cuboidal epithelium. This was surrounded by a moderate number of proliferated ependymal cells. The epithelial layer of the central canal was broken at the lateral edges. The cavities were lined by a minimal number of glial cells and a few proliferated and reactive blood vessels. The anterior spinal veins were minimally dilated.

In the lumbar region there was a bilateral descending demyelination. The commissural fibers were intact. The central canal had two lumens, and there were a small number of proliferated ependymal cells nearby. The commissural region was wider than usual, but the parenchyma was not destroyed.

Comment.—The pathologic findings were typical of syringomyelia. The occasional intimate relation between hydromyelia and syringomyelia was noted. The loss of vibratory sense was more extensive than could be explained by the age of the patient. There seemed to be a correlation of motor signs, loss of vibratory sense, and disorders of the lateral columns. On the other hand, relatively intact posterior columns and preservation of position sense were noted.

Case 8.—L. R. was a 50-year-old man whose illness began with pain in the lumbar part of the spine. There was a relatively rapid progression of symptoms at first but little change in the subsequent 17 years. The case has been reported by Schlezinger and Ungar,[8] and for full details their report may be consulted. It is of interest that the patient had some diminution of vibratory sense in all four extremities, but position sense was unimpaired. It was thought that a syrinx had formed near one of the vertebral hemangiomas because of the peculiar blood supply of the cervical region. The presence of "islets of vessels with hypertrophied adventitia" was described and pictured. A review of the microscopic material reveals that there were malformed or hemangiomatous vessels within, as well as outside, the spinal cord. The present interpretation is that these malformations, which were similar to the vascular changes in the vertebrae, were the cause of syringomyelia in this case, rather than a peculiarity of blood supply.

It should be noted that of the 33 cases of vertebral hemangioma with spinal cord symptoms reviewed by Schlezinger and Ungar,[8] this case was the only one with syrinx formation. Indeed, in this case, the upper vertebrae contained hemangiomas, but syrinx formation was absent. The explanation is offered that in most cases of vertebral hemangioma there is no extension of the abnormal vessels into the spinal cord.

COMMENT

Clinical Aspects.—At the onset of syringomyelia, diagnosis may be difficult. An extramedullary lesion is suggested when the onset is associated with severe pain. With the passage of time, evidence of intramedullary disease becomes more apparent. If the motor signs at the onset are limited to a single extremity, a focal lesion, such as cervical rib, is suggested. Indeed, there are some patients in whom these two disorders appear together. The syrinx rarely remains limited, however, and other signs eventually become apparent. In the early stages, the diagnosis of multiple sclerosis may be considered. This is especially true because a long syrinx may suggest disseminated lesions and because some patients with syringomyelia may

8. Schlezinger, N. S., and Ungar, H.: Hemangioma of the Vertebra with Compression Myelopathy, Am. J. Roentgenol. **42**:192-216, 1939.

complain early of cranial paresthesias, blurred vision, and diplopia. The latter symptoms soon fade away, frequently never to recur, but the evidence of a remission may continue to suggest a diagnosis of multiple sclerosis. The course of syringomyelia is long, usually 10 to 15 years, but cases have been reported of courses lasting up to 50 years. A protracted course may occur even in cases of syringobulbia. The symptoms frequently progress for a few years and then remain static for the rest of the life of the patient, or there is slow, and intermittent or continuous deterioration. The ultimate findings of decrease or absence of pain and thermal sensation with intact touch sensation, the presence of local paralyses, with fasciculations and atrophies, and the frequent spastic weakness of the lower limbs associated with trophic and skeletal alterations form the typical picture of syringomyelia. Other types of sensory dissociation may occur, most commonly early in the disease. Thus, as illustrated in Cases 3, 4, and 5, temperature sensation may be more affected than pain; heat sensation more than cold, or the reverse may be true. In these instances it is suspected that there is a different sensitivity of the fibers or that some form of functional lamination exists. In addition, some of the present cases indicate that vibratory sense may be altered, with preservation of position sense. As discussed below, this dissociation may be related to anatomical separation of fibers subserving these functions. Intact sensation of the buccal mucosa with analgesia on the face was noted in one case.

It is well recognized that this clinical picture may occur with other intramedullary disease. In the case of hematomyelia, the history of trauma and the continued resolution of the symptoms easily differentiate it from most instances of syringomyelia. Differentiation from intramedullary neoplasms is much more difficult and frequently is made on the basis of a more rapid progression of the symptoms of tumor than of syringomyelia. Accumulation of recent data casts doubt on this differential point in many instances. Woltman, Kernohan, Adson, and Craig[9] have demonstrated many cases of survival of 10 and 20 years' duration with ependymomas of the spinal cord. In 26 cases the total duration averaged 12.2 years, the longest being 36 years. The diagnosis of intraspinal neoplasm, therefore, cannot be ruled out because of the slow progress or long duration of the disease. Study of the cerebrospinal fluid sometimes is helpful in this differentiation, for increases of protein and evidence of spinal fluid block are found oftener with tumor; but these may be observed in some cases of syringomyelia and may be absent with tumor. Neoplasms more commonly result in focal transverse myelitis, but this does not always occur. Most other differential diagnoses are made easily, especially after continued observation; but separation of syringomyelia from some intramedullary neoplasms is most difficult.

Dissociation of pain and temperature from touch sensation is related to transection of the decussating spinothalamic fibers in the ventral commissure. Dissociation of vibratory and position sense, to the best of my knowledge, has been described in syringomyelia only in the two cases of Laidlaw, Hamilton, and Brickner.[10] It was surprisingly common in the cases reported here. The dissociation is a well-known finding in a variety of other disorders,[11] and hence is not diagnostic, although

9. Woltman, H. W.; Kernohan, J. W.; Adson, A. W., and Craig, W. M.: Intramedullary Tumors of Spinal Cord and Gliomas of Intradural Portion of Filum Terminale: Fate of Patients Who Have These Tumors, A. M. A. Arch. Neurol. & Psychiat. **65**:378-395, 1951.

10. Laidlaw, R. W.; Hamilton, M. A., and Brickner, R.: The Occurrence of Dissociated Disturbances of Pallesthesia and Kinesthesia, Bull. Neurol. Inst. New York **7**:303-320, 1938.

11. Fox, J. C., Jr., and Klemperer, W. W.: Vibratory Sensibility: A Quantitative Study of Its Thresholds in Nervous Disorder, Arch. Neurol. & Psychiat. **48**:622-645, 1942.

in the absence of peripheral neuropathy it suggests intramedullary disease. In explanation of the dissociation, it is assumed that there are separate pathways in the posterior columns, or that there are separate pathways elsewhere in the spinal cord. The second explanation is usually disregarded, and it is widely accepted that "posterior column signs" include both modalities.

The findings presented here offer strong support for the location of pallesthetic fibers in the lateral columns. This assumption is based, first, on the surprisingly common finding of the dissociation (Cases 1, 3, 4, 5, 7, and 8) early in the course. In these instances vibratory sense was impaired while position sense was intact. The finding is not explained by the age of the patients, although in all but Case 5

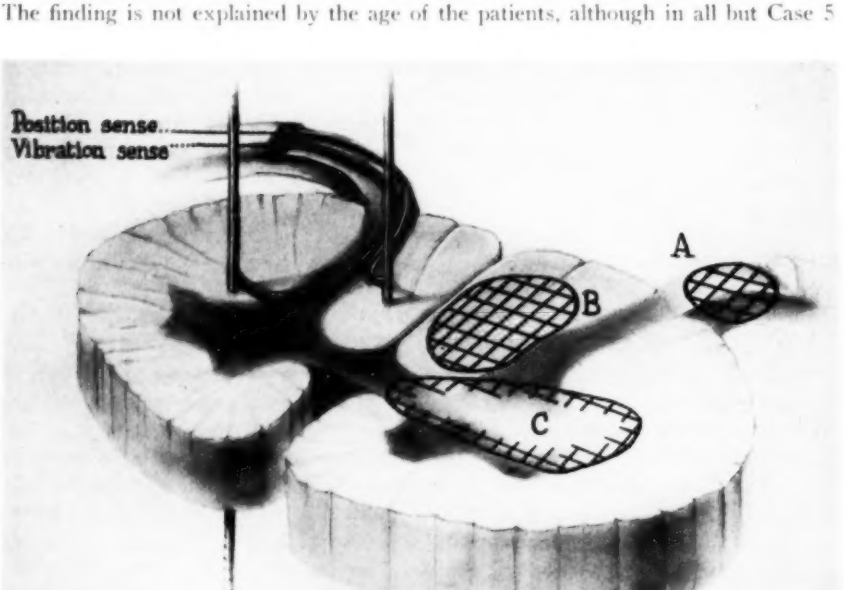

Fig. 22.—The hypothesis of separation of fibers subserving vibratory and position senses is schematically illustrated. The lesion at *A* demonstrates how the usual diseases of posterior roots, such as tabes dorsalis, may result in alterations of both types of sensation. At *B*, a lesion, such as a plaque of multiple sclerosis, results in loss of position sense alone. The lesion at *C* shows the frequent location of a syrinx, causing loss of sense of vibration with preservation of position sense.

(age 24) the patients were about 50 years of age. With increasing age, such dissociation is noted bilaterally in the feet and up to the iliac crests, but not in the hands. In the present cases, the loss was general, in the hands, or unilateral.

Second, loss of vibratory sense was in all instances more closely associated with lower or upper motor neuron signs than with position sense. Thus, in Case 3 both upper extremities were atrophic, and vibratory sense was lost in these regions. In Case 5 an initial right hemiplegic form of syringomyelia was accompanied by loss of vibration sense on the right side; and when the left side became weak, pallanesthesia became apparent on that side.

Case 3 is a crucial one in this contention. In the other cases the progression of the disease was such that position sense ultimately was affected, and at necropsy there was found implication of the lateral columns and at least partial destruction of the posterior columns. But in Case 3 vibratory sense was altered only in the upper extremities, which were the site of atrophy and fasciculations. The condition remained static for two years, and death was the result of pulmonary tuberculosis. Anatomically, the posterior columns were intact, but demyelination was present in the lateral funiciulus adjacent to the destroyed anterior horns. This case, therefore, strongly suggests that vibratory sense is carried in pathways in the medial part of the lateral funiculus (Fig. 22).

If this idea is correct, why has it not been recognized? The assumption that pallesthesia and kinesthesia are related to the posterior columns is based largely on their association in disorders such as tabes dorsalis, subacute combined degeneration, and Friedreich's ataxia. Posterior root affection is common to these conditions, and the loss of both types of sensation probably is related to implication of the large myelinated A and B fibers in the root. On the other hand, dissociation with either pallanesthesia or kinanesthesia is not uncommon in multiple sclerosis.[10] This is easily understandable if the present theory is accepted, because pallanesthesia would be related to a plaque in the mediolateral column and kinanesthesia to a plaque in the posterior column. Chordotomy does not affect vibratory sense [11] because the incision involves only the periphery of the lateral column and its more anterior portions. Descending degeneration of the pyramidal tracts, as in amyotrophic lateral sclerosis, does not result in pallanesthesia because the fibers of vibratory sensation are close to the gray matter.

The possibility remains, however, that there is a difference in sensitivity of pallesthetic and kinesthetic fibers to noxious agents. This cannot be excluded by the present data. It should be noted that studies of conduction in peripheral nerves have shown that both types of sensation are carried in similar large myelinated A and B fibers. Dissociation may occur in instances of peripheral neuropathy. Differential sensitivity would not explain the fact that either position sense or vibration sense alone may be lost in multiple sclerosis. Nor would it explain the frequent relation of motor signs and vibratory sense.

TREATMENT OF SYRINGOMYELIA

Review of the methods of treatment discloses some interesting facts. It is found that roentgen therapy is considered of value in about 60% of cases.[12] This occurs in large series regardless of the age or sex of the patient or the duration and extent of the disease. Improvement is often obtained without regard to the method of x-ray treatment.[13] Of further interest is the fact that surgical treatment is effective in approximately the same percentage of cases and also is independent of any clinical factors.[14] The consistency of the figures suggests that psychogenic factors may play

12. O'Brien, F. W.: Roentgen Therapy in Syringomyelia, Radiology **24**:16-21, 1935.

13. Haworth, E. M.: Treatment of Syringo-myelia by X-Rays, Brit. J. Radiol. **1**:643-653, 1934.

14. Frazier, C. H., and Rowe, S. N.: The Surgical Treatment of Syringomyelia, Ann. Surg. **103**:481-496, 1936.

a role. There have been no controlled studies of syringomyelia, using sham radiation with filters to eliminate the x-rays. Sham radiation might have as much subjective value as genuine radiation. Most of the value attributed to x-ray treatment has related to subjective complaints. Improvement of skin circulation by erythema-producing doses is, of course, transient and of no conceivable value for the underlying disease. It is unfortunate that any improvement after x-ray therapy is attributed to such treatment but continued complaints of the patients are attributed to the course of the disease. It is, furthermore, difficult to discover a rationale for x-ray therapy. Gliosis, cavitation, and malformations of mature blood vessels are the substrate of syringomyelia. There is no evidence that any of these are benefited by x-ray therapy. On the contrary, the possibility of radiation myelitis is a definite one,[15] and gliosis may be speeded. It is therefore possible that x-rays are harmful, but that the deleterious effects are masked by the progression of the disease. Occasionally patients may complain of being made worse (Case 5).

Surgical incision of the cavity probably is also of little value, and a similar lack of controlled observations is apparent in most reports. The exception is the rare case in which there is blockage of the cerebrospinal fluid circulation. It is justifiable to assume that at least temporary improvement results from release of the block, but the basic disease process is unaltered.

ASSOCIATION OF SYRINGOMYELIA WITH VASCULAR MALFORMATIONS AND NEOPLASMS

There is an unusually high coincidence of syrinx formation and intramedullary vascular masses, including malformations or true new growths. In 20 of 26 cases (77%) syringomyelia was associated with an intramedullary hemangioblastoma.[16] Syringomyelia does not occur when the same tumor occurs outside the cord substance. Wyburn-Mason[16] has presented evidence indicating that syringomyelia is an integral part of Lindau's disease, although the syrinx may be asymptomatic and not discovered unless the spinal cord is examined at necropsy. Malformations of the blood vessels of the spinal cord, when intramedullary, also have a high incidence of associated syringomyelia (Cases 7 and 8 reported by Brion, Netsky, and Zimmerman[17]). It is also true that primary neoplasms of the spinal cord may be associated with syringomyelia, but the incidence is lower. Wyburn-Mason cited 11 instances of syrinx formation in 25 cases (44%) of primary intramedullary neoplasms. The incidence at Montefiore Hospital in a smaller series was only 25%, representing two of eight cases. In these instances the cavities were histologically indistinguishable from those of "true" syringomyelia.

The present interpretation is that syringes occur in association with intramedullary neoplasms on the same basis as in "true" syringomyelia (see "Pathogenesis"). In the two cases at this hospital in which this combination occurred, abnormal numbers of unusually large vessels were found near the cavities. This explains the association when it occurs and, on the other hand, it helps to explain the more frequent absence of syringomyelia in instances of intramedullary gliomas.

15. Boden, G.: Radiation Myelitis of the Cervical Spinal Cord, Brit. J. Radiol. **21**:464-469, 1948.

16. Wyburn-Mason, R.: The Vascular Abnormalities and Tumors of the Spinal Cord and Its Membranes, London, Henry Kimpton, 1943.

17. Brion, S.; Netsky, M. G., and Zimmerman, H. M.: Vascular Malformations of the Spinal Cord, A. M. A. Arch. Neurol. & Psychiat. **68**:339-361, 1952.

Vascular malformations and vascular neoplasms will have concurrent syringomyelia oftener because abnormal vessels are more likely to extend into nearby tissue. In the case of gliomas, there are as yet no data to help decide whether the abnormal vessels are present from birth or whether they arise later as part of the growth of the neoplasm. Nevertheless, when syringomyelia occurs in association with a glioma, malformed and abnormal numbers of blood vessels may be found in and around the syrinx.

PATHOGENESIS OF SYRINGOMYELIA

Cavitation in the spinal cord, usually (although not always) associated with gliosis or fibrosis, is the pathologic mark of syringomyelia. If infarcts, old inflammations, etc., are found with syrinx formation, the cavity should be diagnosed as part of the recognized basic disease. There remains, then, an unexplained group designated as "true" syringomyelia. Hydromyelia is used conventionally to designate a simple dilatation of the central canal, usually silent clinically. Actually this sharp separation is an oversimplification, although it is frequently valid. Hydromyelia may be an unexpected finding in routine examinations of the spinal cord, but so, too, may syringomyelia (Case 2). Hydromyelia not only may accompany syringomyelia but may in some instances (Case 7) be an intimate part of the syrinx. On the other hand, a normal undilated central canal often is found at the same level as a large syrinx. Therefore, it cannot be argued that further dilatation of a hydromyelic cavity is the usual origin of syringomyelia.

The central canal or rests of ependyma play an important role in the theory that cavities form from embryonic cell rests.[18] The theory states that cavities arise in gliotic tissue within ependymal cell rests and hence the disease is a developmental anomaly related to imperfect formation of the central canal. The theory is further supported by the finding of ependymal linings in cavities.

It has been shown in the section on "Development of the Spinal Cord" that many of these so-called congenital rests are actually acquired alterations. Ependymal cells can proliferate in response to various disorders and may well be the result of cavitation rather than the origin or cause. Furthermore, it is commoner to find syringes without ependymal lining and with wholly intact and normal central canals. The ependymal cell rest theory does not account for the frequent finding of cavities in the dorsal parts of the posterior horns, a region where rests of ependyma are never found.

It is often argued that the origin of syringomyelia as a malformation is supported by the occurrence of the disorder in patients with evidence of dysplasia. The dysplastic person may have cervical ribs, web fingers and toes, sternal anomalies, inequality of mammary development, etc.[19] Some of the described defects may be acquired, such as kyphoscoliosis and talipes. The line between these anomalies and physiologic variants is difficult to draw. In Schlesinger's large series, there were only 33% with anomalies, the majority lacking these. The same anomalies occur in persons without syringomyelia. It may be concluded that a truly "dysplastic" person more likely has a syrinx if spinal or bulbar symptoms develop, but such dysplasia is too often lacking to offer a valid basis for a general theory.

18. Tamaki, K., and Lubin, A. J.: Pathogenesis of Syringomyelia: Case Illustrating the Process of Cavity Formation from Embryonic Cell Rests, Arch. Neurol. & Psychiat. **40**:748-761, 1938.

19. Riley, H. A.: Syringomyelia or Myelodysplasia, J. Nerv. & Ment. Dis. **72**:1-27, 1930.

The extension of the malformation theory states that ependymal cell rests or errors in the closure of the neural tube are the cause of syringomyelia. The ependymal cell rest theory has been discussed, and reasons have been offered for its lack of validity. The theory that a simple error in the closure of the neural tube is responsible for syringomyelia cannot be given much credence. Most congenital anomalies affecting the spinal cord occur at one end or the other of the spinal column; for example, the Arnold-Chiari malformation occurs at the rostral end, and spina bifida oftenest affects the caudal end. Syringomyelia is commonest in the cervical and lumbar portions of the spinal cord. Closure of the neural tube occurs in the midline and in the anteroposterior plane. Syringes most commonly lie at right angles to the line of closure. Syringes frequently occur in the posterior horn at relatively great distances from the line of fusion and the central region. In the brainstem, cavitation is commonest away from the midline. Furthermore, gray matter is the predominant site of cavitation, white matter usually being implicated only by extension; this cannot be explained by the manner of closure of the neural tube. It is difficult to understand the late onset of the disorder if failure of closure is the cause. Malformations, such as spina bifida and the Arnold-Chiari syndrome, usually are evident early in life. It is exceedingly rare for syringomyelia to occur before the age of 10 and in most cases it is found after the age of 20.

From the data presented it is suggested that an intramedullary vascular anomaly of the spinal cord is the cause of "true" syringomyelia. This conception is based on the following considerations, which are here tabulated:

1. In instances in which other anomalies of the body occur, spinal vascular anomalies often may be found.

2. There is a high correlation between intramedullary vascular malformations and vascular neoplasms, and syringomyelia.

3. The cervical and lumbar regions are best vascularized and are oftenest the site of syrinx formation.

4. Gray matter is more vascular than white matter and is the predominant site of syringomyelia. The posterior horn is often affected, as is the posterior median septum; and these locations often contain anomalous vessels.

5. Anomalous vessels frequently are found in and around "true" syringes.

6. Gliosis often is an accompaniment of or a reaction to abnormal vascularization.

7. The large amount of connective tissue which occurs in some syringes is best explained as originating from an increased number of blood vessels. Such connective tissue proliferation may occur in unirradiated patients (Case 2).

8. Vascular hemorrhages and occlusions and physiologic alterations of blood flow, with slow reactive repair of damage, account for an initial rapid onset of symptoms, subsequent quiescence, and/or progressive disease. Reactive gliosis and fibrosis may be correlated with slow progression.

9. The effects of vascular anomalies frequently occur later in life, as does syringomyelia.

The following general theory of pathogenesis is offered. The patient is born with intramedullary vascular anomalies, which, in the course of time, become occluded or ineffective for maintenance of circulation. This leads to tissue destruction and cavitation, followed in some instances by a reparative gliosis or connective tissue pro-

liferation. As a result, the anomalous vessels themselves may be infarcted, ultimately leaving only a cavity; but usually a few large abnormal vessels may be seen. Occasionally true vascular new growths may occur in these abnormal vessels. With loss of the majority of vessels, the condition then remains quiescent, or slowly progressive as gliosis or fresh occlusions occur.

SUMMARY AND CONCLUSIONS

Eight cases of syringomyelia are presented with necropsy. Some patients were observed for as long as 20 years. The course frequently is stormy for a few months or years, and the disease then becomes quiescent or only slowly progressive. Intramedullary neoplasms of the spinal cord constitute the chief diagnostic difficulty. Many types of sensory dissociation may be encountered in syringomyelia. In addition to the commonplace loss of pain and temperature sensation with preservation of touch: heat and cold sensation, pain and temperature sensibility, and vibratory and position sensation may be dissociated. There was loss of vibratory sensation with intact position sense early in the course in six of eight cases. Evidence is presented to show that pallesthetic fibers may not be situated in the posterior columns, but, rather, may lie in the medial portion of the lateral columns.

Treatment of the disease is wholly unsatisfactory. There have been no controlled experiments to determine the value of x-ray therapy or of surgery. The symptomatic improvement occasionally obtained may well be psychogenic. X-ray therapy lacks a rationale and, indeed, may be harmful.

It is shown that the central canal of the adult cord frequently is the site of a disorderly proliferation of ependyma. This contrasts with the single layer of epithelium found in the infant. It is concluded that such ependymal proliferation is an acquired variant rather than a congenital rest. Current ideas of the pathogenesis of syringomyelia are discussed, and a general theory of the pathogenesis of the disease is offered. This theory relates the developmental origin of the disease to anomalies of the intramedullary blood supply. When the patients reach adult life, vascular insufficiency and occlusions lead to cavitation, gliosis, and fibrosis. The theory is considered in relation to, and accords satisfactorily with, the clinical data, the location of the lesion, the pathologic findings, and the common association of this disorder with intramedullary hemangioblastomas.

Mr. Antol Herskovitz prepared the photomicrographs.

AUTONOMIC RESPONSES IN DIFFERENTIAL DIAGNOSIS OF ORGANIC AND PSYCHOGENIC PSYCHOSES

WILLIAM G. REESE, M.D.
LITTLE ROCK, ARK.
RICHARD DOSS, M.D.
AND
W. HORSLEY GANTT, M.D.
BALTIMORE

I. STATEMENT OF THE PROBLEM

DURING the past half-century, since the discovery of the conditional reflex [1] by Pavlov, a wealth of material has been accumulated from the study of the behavior of animals by this means. Nearly every important organ of the body has been investigated, chiefly in dogs, from the point of view of the animal's ability to form new stimulus-response patterns on the basis of individual experience. The published material is abundant, notwithstanding the lack of its availability in the standard medical and physiological texts.

Relatively little, however, has been published regarding the results of such studies on the human being. A great deal has been written of a general discursive nature regarding human conditional responses, much of it under the broad designation of "behaviorism," but the interest in that approach to psychology has fallen off because too much was claimed for it in broad general terms. Not much human experimentation on conditional responses has been done in a manner to permit clear-cut conclusions and direct comparison with the results of animal experiments. Nevertheless, a few useful applications of this objective methodology to the human being have been made. Among these in the United States have been the evaluation of hearing in infants by Bordley and associates [2] through a psychogalvanic condi-

From the Psychophysiological Laboratory, Veterans Administration Hospital, Perry Point, Md.

The statements and conclusions of the authors do not necessarily reflect the opinion or policy of the Veterans Administration.

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1. The abbreviation CR, or its plural form CR's, is used in this paper for "conditional response(s)." It may be read "conditional reflex" when there is clear proof that the response on which it is based is a simple, innate reflex, but this question of pure innateness is not a primary issue in the study here reported. Other abbreviations used in this communication are UR, for unconditional response; US or USi, for unconditional stimulus or stimuli; CS or CSi, for conditional stimulus or stimuli, and OR, for orienting response.

2. Bordley, J. E.; Hardy, W. G., and Richter, C. P.: Audiometry with the Use of Galvanic Skin-Resistance Response: Preliminary Report, Bull. Johns Hopkins Hosp. **82**:569, 1948.

tional response, and the study of the motor CR's in psychiatric patients by Gantt, Muncie, and us.

The studies of the motor conditional response by Gantt[3] and Gantt with Muncie,[4] Fleischmann,[5] and Fleck,[6] at the Phipps Psychiatric Clinic, have revealed interesting characteristics of psychiatric patients and pronounced differences between the psychogenically and the organically determined psychoses. Patients with organic psychoses, such as Korsakoff's alcoholic dementia, severe cerebral defects, and certain temporary cerebral disturbances, such as those after some shock treatments, when studied in this way, have been found to be deficient in the ability to form conditional responses, while patients with psychogenic psychoses, even severe conditions, such as catatonic schizophrenia, have been found to retain this ability. Such observations make it possible to use a modified conditional reflex examination as a means of differentiating the organic and the psychogenic psychoses. In the study of the psychiatric patient by the Pavlovian method, moreover, interesting mechanisms were revealed that were not apparent with the ordinary methods of psychiatric study. Thus, the catatonic patient is capable of forming conditional responses, although general inhibition in the motor system obscures their appearance; i. e., the catatonic patient is adaptive to his environment in a manner that the organic patient is not.

In spite of the technical ease of forming and detecting motor CR's in the normal subject, there are certain inadequacies in the use of the motor system alone in these studies, and several advantages are to be gained by an inclusion of the autonomic responses (cardiac, respiratory, psychogalvanic), generally considered more intimately related to emotional states.

A simultaneous recording of motor and autonomic responses would not only afford correlations of the different systems but might give an insight into what occurs on the unconscious level, where physiological events are not visible to the subject or under his direct "voluntary" control, as are the skeletal movements. Such parallel studies in the dog have already uncovered important mechanisms not apparent in the consideration of the motor behavior only.[7] Thus, a comparison of

3. Gantt, W. H.: (*a*) An Experimental Approach to Psychiatry, Am. J. Psychiat. **92**:1007-1021, 1936; (*b*) Application of Conditioned Reflex Methods to Psychiatry, Johns Hopkins Press, 1937, pp. 78-80; (*c*) A Method of Testing Cortical Function and Sensitivity of the Skin: An Aid in Differentiating Organogenic and Psychogenic Disturbances, Arch. Neurol. & Psychiat. **40**:79-85, 1938; (*d*) Impairment of the Function of Adaptability as Measured by a Simple Conditioned Reflex Test in Certain Psychogenic Contrasted with Organic Diseases, South. M. J. **31**:1219-1225, 1938; (*e*) The Conditional Reflex Function as an Aid in the Study of the Psychiatric Patient: Relation of Psychological Tests to Psychiatric, New York, Grune & Stratton, Inc., 1950.

4. Gantt, W. H., and Muncie, W.: Analysis of the Mental Defect in Chronic Korsakov's Psychosis by Means of the Conditioned Reflex Method, Bull. Johns Hopkins Hosp. **70**:467-487, 1942.

5. Gantt, W. H., and Fleischmann, W.: Effect of Thyroid Therapy on the Conditional Reflex Function in Hypothyroidism, Am. J. Psychiat. **104**:673-681, 1948.

6. Fleck, S., and Gantt, W. H.: Conditional Responses in Patients Receiving Electric Shock Treatment, Am. J. Psychiat. **108**:280, 1951.

7. Studies of cardiac reactions in relation to motor and secretory conditional reflexes have been made in the dog (Gantt and others) and in the normal human (Gantt, Dykman, and Peters). In the dog, particularly, the changes in heart rate provide a sensitive indication of autonomic reactions occurring with systematic regularity in orienting (or questioning) behavior and in the learning of motor and salivatory conditional responses.

the cardiac (emotional?) components and the motor component of the CR in the dog shows that the organism may retain responses in one system—the cardiac—years after it has lost the more specific skeletomotor aspects of the CR.[8]

Another question of interest was this: Is it only on the voluntary motor level that the conditional response is given to a stimulus involving a slight emotional disturbance, or does the subject's reaction always involve other responses not present in consciousness, e. g., the cardiac and the psychogalvanic? Also, when the patient fails to show the motor CR, is there a corresponding failure in the autonomic measures? Not only are answers to these questions of diagnostic value, but they might throw light on the correspondence between observable, "voluntary" movements and the unconscious, autonomic aspects of the behavior.

Because of the lack of adequate apparatus, the simultaneous study of additional autonomic components at the Phipps Clinic had been limited. Establishment in 1950 of a well-equipped laboratory at the Veterans Administration Hospital, Perry Point, Md., has made possible the present investigation of the autonomic responses accompanying motor conditioning.

II. APPARATUS

The apparatus consists of signaling devices for conditional stimuli (colored electric light), an electric circuit for the unconditional stimulus (slight electric shock), and the recording unit—the Darrow photopolygraph. The control mechanism is a device which can present the conditional stimulus (CS) and the unconditional stimulus (US) automatically at precise intervals. This is done by eccentric cams mounted on a shaft from a 1-rpm constant speed motor.[9] Separate cams close apposing microswitches for the periods of the conditional stimulus and the unconditional stimulus in their proper relationships and record simultaneously these events on the photopolygraph.

The electric circuit for the unconditional stimulus consists of a variable transformer in circuit with the hand electrodes for administering the slight electric shocks. This transformer is used to determine the threshold of sensation and that of pain for each subject and is set at a level which is slightly painful for the particular subject. Within this electric circuit, there is a short circuit for use by the subject in avoiding the electric current in the latter part of the test. This occurs through a microswitch below the tremograph. When this is closed, the electric current is by-passed from the electrodes.

The recording unit is a Darrow photopolygraph, which records in their exact temporal relationship the skin resistance, respiratory movements, movements of both hands, the heart rate, and the signal markers for the CSi and the US.

III. PROCEDURE AND SUBJECTS

The general procedure has been described in the previously mentioned references.[3e] This was used, with certain modifications, in the present test.[10]

Six patients and eight normal subjects were studied, with recordings of heart rate, chest movements, skin resistance, spontaneous hand movements, and integrated hand movements.

8. Gantt, W. H.: Psychosexuality in Animals: Psychosexual Development in Health and Disease, New York, Grune and Stratton, Inc., 1949, pp. 33-51; Principles of Nervous Breakdown—Schizokinesis and Autokinesis, Ann. New York Acad. Sc. **56**:141-380, 1953.

9. This automatic timing device was constructed by Dr. Charles Strahan in this laboratory (Reese, W. G.; Gantt, W. H., and Strahan, C.: Technique for Study of Automatic [Cardiac, respiratory, PGR] and Motor Adaptive Responses [CRS] in the Human, Am. J. Psychiat. **163**:744, 1950). Dr. Cecil Reese aided materially with the technical aspects of the apparatus.

10. Extreme groups were used in the study, making it unnecessary to go through Gantt's detailed scoring procedure.

Integration on the simple symbolic level was studied in terms of degree of adaptiveness of motor responses and, on a more complex level, in terms of verbalization of the simple controlled experience.

The six patients could be classified under the general heading, "psychotic disorders with demonstrable physical etiology or associated structural changes in the brain, with moderate to severe changes in intellectual functioning." The series included one woman in her 70's, four men in their 50's, and 1 man aged 38. The diagnoses were cerebral arteriosclerosis, two patients; dementia paralytica with cerebral arteriosclerosis, one patient; Korsakoff's psychosis, two patients, and insulin shock encephalopathy with schizophrenia, one patient. These patients had in common evidence of diffuse cortical damage, manifested by pronounced impairment of recent memory, as contrasted with good or fair past memory; by impairment of attention; by disorientation, particularly in the temporal sphere, and by a variety of mild disturbances of mood. Electroencephalographic reports (Dr. W. Oppler) were available for three: C. W., normal; E. A., S-1, activity; F. S., fast, diffuse activity with spikes. All these patients were cooperative and could follow simple instructions. (See appendix for brief clinical sketches of these patients.)

The normal group consisted of eight professional men, who, with one exception, were without knowledge of the procedure.

IV. RESULTS

Below will be found a description of both the unconditional and the conditional responses in normal subjects and in patients. The results in the two groups are summarized in Tables 1 and 2 and in Figures 7 and 8.

Unconditional Responses

General Reactions.—Each patient was tested two or three times at intervals of longer than a week. It was not our purpose to determine whether or not conditioning could be accomplished with a large number of trials.[11] At the time of the retest, all but one of our patients recalled appropriately, although vaguely, having previously been tested. The patient who did not remember previous tests seemed somewhat reluctant about reentering the test room but could not say why. She was the only patient who regularly pulled her fingers from the electrode-bearing tremograph with the current, and she alone continued beyond the first few trials to startle to the US. The other patients complied with the procedure and returned for retest without apparent reluctance.

The "normal" subjects were not strictly volunteers but were requested to participate. Only one of these found reasons for postponing his participation. All of them were interested in the procedure, and after the procedure each asked how he had done. Only one normal subject exhibited general evidence of apprehension. He interpreted the procedure as a test of his ingenuity in manipulatively avoiding the shock. Thus, he attempted to avoid the shock by closing the partially visible microswitch in varying temporal relationships to the light signals. This avoidance circuit was broken at the experimenter's control panel, so that the subject could not succeed. In the post-test interview, he reported a mounting feeling of frustration during the conditioning procedure, followed by a feeling of resignation.

Motor Components.—All the patients and the subjects responded to the actual electric current with a quick, small withdrawal motion of the stimulated hand,

11. Tatarenko, in 1935, reported that CR's could not be formed in senile psychotics during 100 to 150 reinforcements (Tatarenko, N. P.: Psychol. Abstr. **9**:757, 1935) and Gantt and Muncie found that, regardless of the number of trials, certain patients with organic brain disorder could not be conditioned.

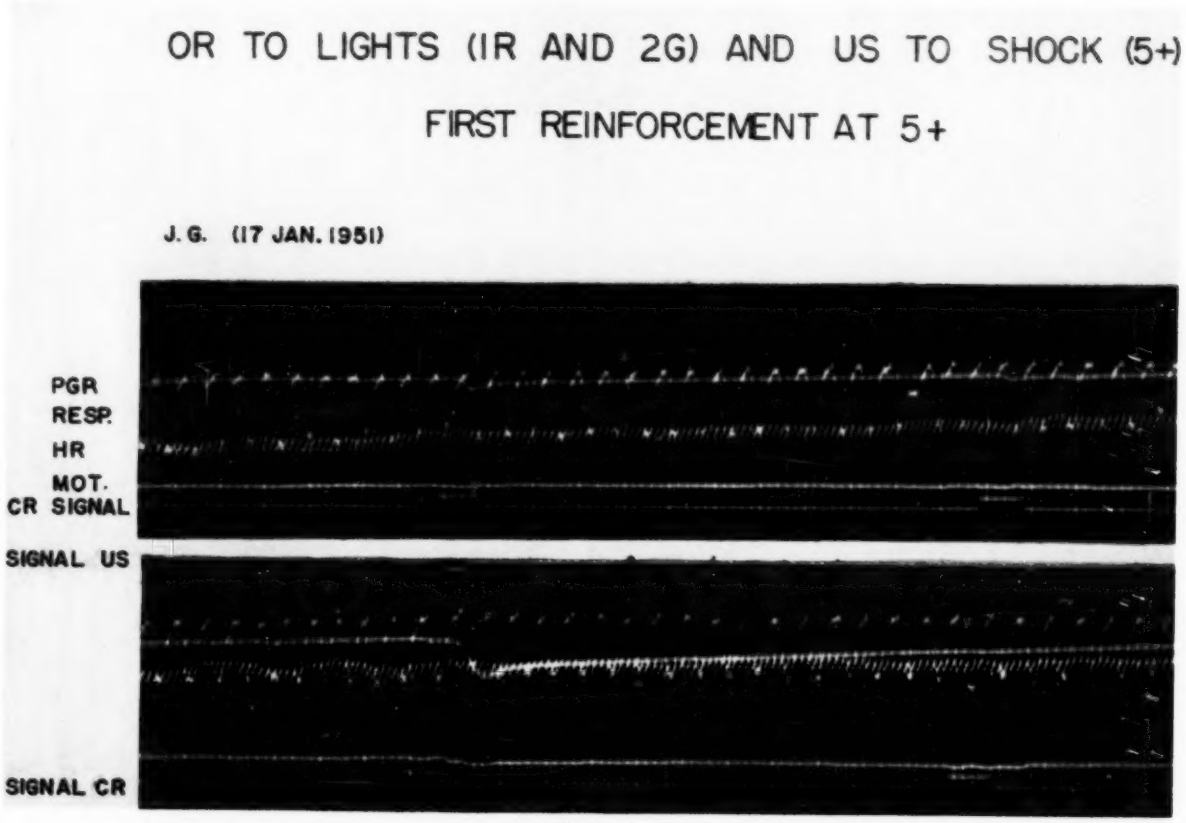
OR TO LIGHTS (1R AND 2G) AND US TO SHOCK (5+)
FIRST REINFORCEMENT AT 5+
J. G. (17 JAN. 1951)
PGR
RESP.
HR
MOT.
CR SIGNAL
SIGNAL US
SIGNAL CR

Figure 1

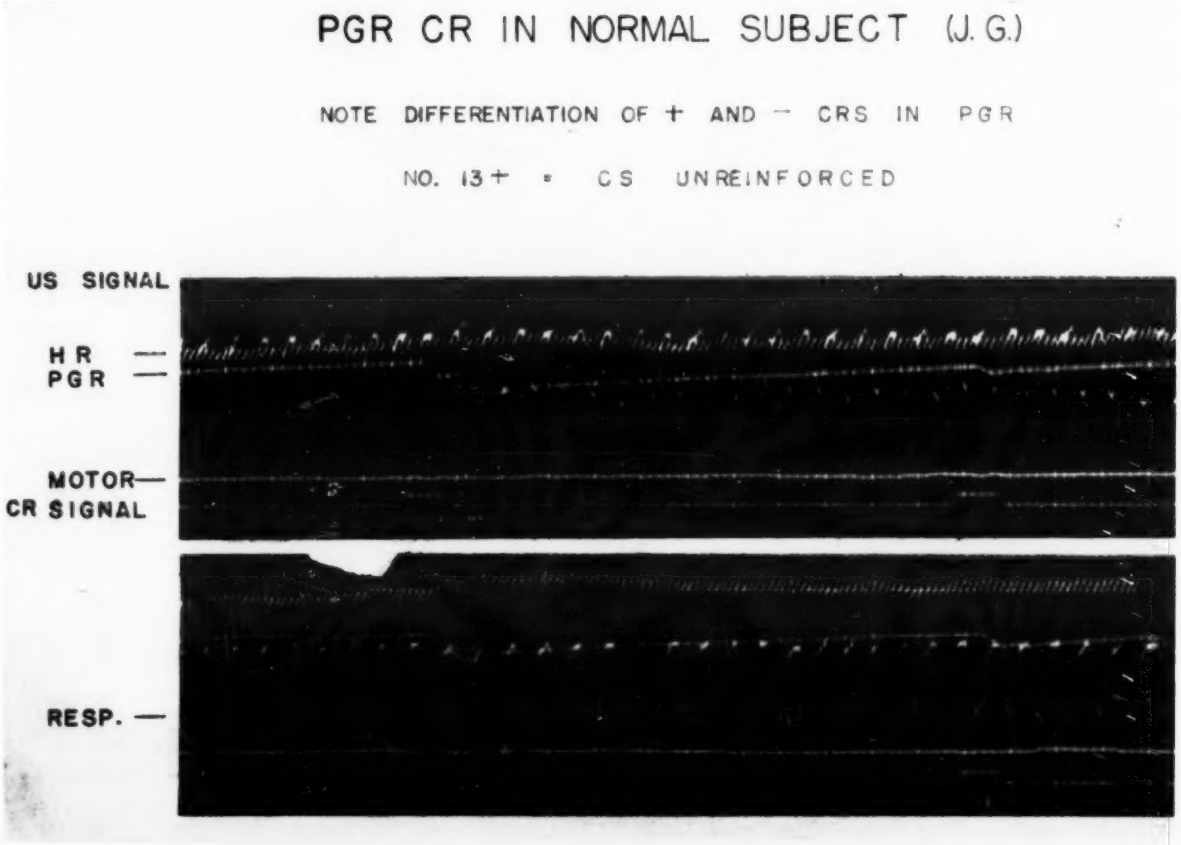
PGR CR IN NORMAL SUBJECT (J. G.)
NOTE DIFFERENTIATION OF + AND − CRS IN PGR
NO. 13 + = CS UNREINFORCED
US SIGNAL
H R
PGR
MOTOR
CR SIGNAL
RESP.

Figure 2

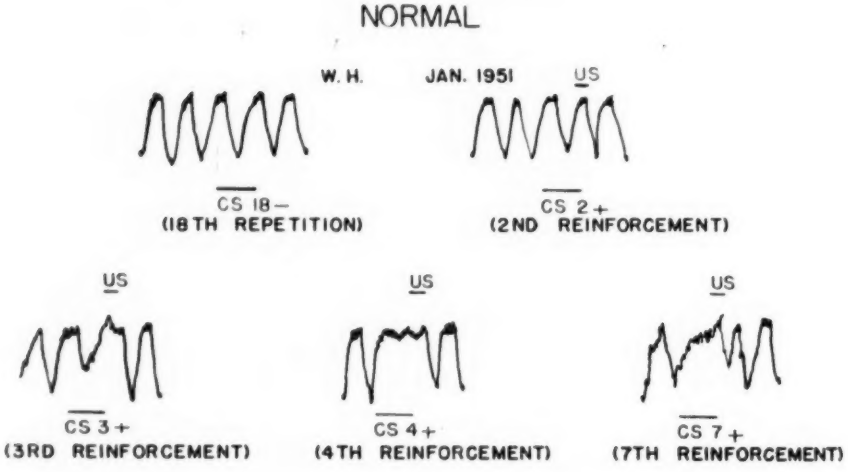

Figure 3

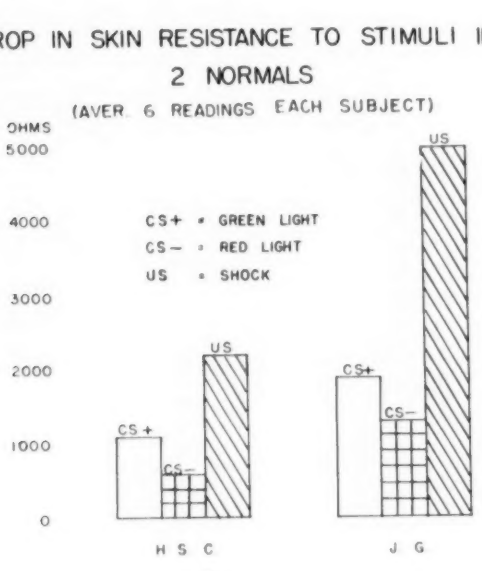

Figure 4

promptly suppressed. They also showed changes in skin resistance, respiratory movements, and irregular movements of the hands. In the normal subjects the avoidance movements were inhibited more than in the patients with organic psychoses—the normal subject rarely removing his hand from the electrode. At times, the movement of the electrode hand was not grossly apparent, but in all instances some movement was unequivocally recorded by the instrument.

Orienting Response.—The orienting response (OR) was present both in normal subjects and in patients (Fig. 1). Insufficient evidence is available at the present time to warrant any definite statement as to the possible difference in OR in the normal subjects and in the patients with organic psychoses. A definite slight movement in the electrode hand was noted in the tremograph during the action of the

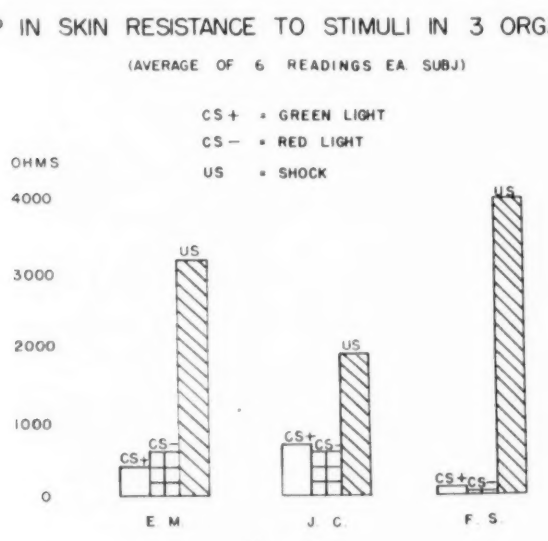

Figure 5

signals to both lights, although there was no movement of the hand visible to the eye. The nature and function of this movement will be reserved for a future study.[12]

Skin Resistance.—There was a drop in the skin resistance in all subjects and patients following the electric shock, with a latent period of approximately two seconds, the range of the drop being about the same in the normal and in the psychotic subjects (Figs. 1, 4, 5, 6, 7, and 8).

Respiration.—Immediately after the electric shock there was a change in respiration in the normal subjects, as well as in the patients. The pattern of the respiratory

12. It appeared, however, that the orienting components were generally less in the subjects with cerebral lesions. If, as Pavlov pointed out by the term "investigatory reflex," and as Whitehorn indicated by the term "questioning response," this pattern of behavior is the basis of investigation and curiosity, it is understandable that it should be lessened in the patient with organic damage. Whitehorn has suggested (personal communication) that this may be closely related to the difficulty of conditioning patients with organic deficit states (Robinson, J., and Gantt, W. H.: The Orienting Reflex (Questioning Reaction): Cardiac, Respiratory, Salivary and Motor Components, Bull. Johns Hopkins Hosp. **80**:231-253, 1947).

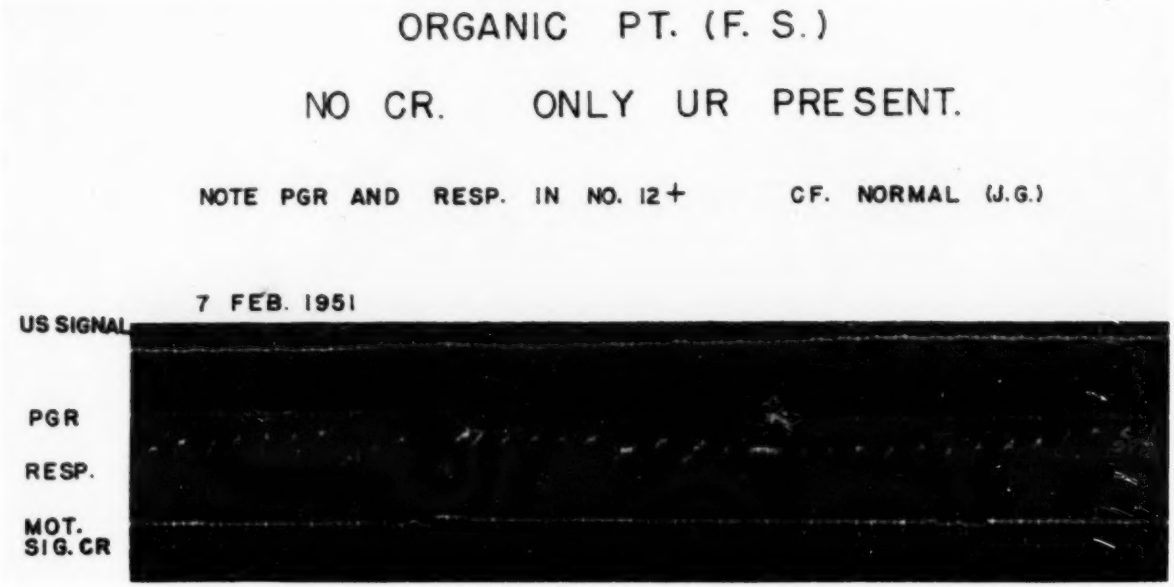
ORGANIC PT. (F. S.)
NO CR. ONLY UR PRESENT.
NOTE PGR AND RESP. IN NO. 12+ CF. NORMAL (J.G.)
7 FEB. 1951
US SIGNAL
PGR
RESP.
MOT.
SIG. CR

Figure 6

movements was consistent in some of the normal subjects but in none of the patients. The changes consisted in holding the breath, a rapid inspiration, or a rapid expiration (Fig. 3).

Heart Rate.—With the low intensity of the electric shock used, there was no significant change in heart rate either in normal subjects or in patients. Detailed[13] counts of records for five normal subjects showed no significant changes in heart

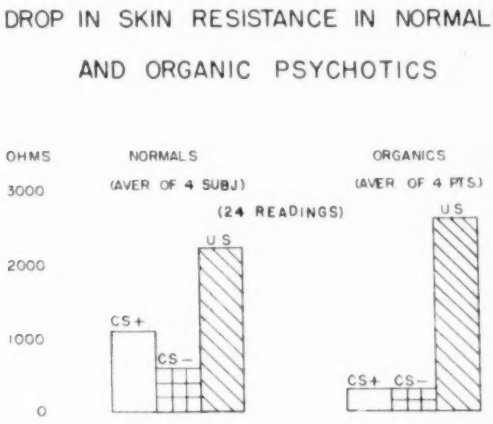

Figure 7

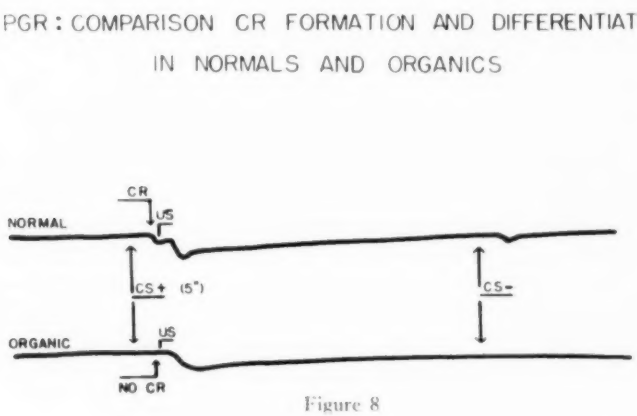

Figure 8

rate caused by the shock. The range of variation in the normal subjects (two to six beats per minute) did not exceed the range of variation in the intervals between signals. For the patients there was no measurable change in heart rate either with

13. Heart rate response was measured in terms of length of time for five consecutive heart beats. Four to six consecutive blocks of five beats during the signal period were measured; in addition, one such block in each five-second period throughout the record was measured. Ease and accuracy of measurement were increased by delineascopic magnification of the record (10 times). Accuracy of reading was about 0.1 second (2 to 3%).

the signals or in the intervals. This may have been due to the short and relatively small shock used or to the fact that the rate changes were too transient to be detected with the method used. Our further studies of cardiac conditioning will include determination of cardiac output and electrocardiographic studies.

Conditional Responses

To judge whether the subject has succeeded in differentiating between the positive and the negative conditional stimuli, one must observe a reliable increase in degree of response to the positive visual stimulus, as compared with the response to the same visual stimulus when experienced before its association with the shock.

The subjects manifest the features of an "orienting reaction" ("questioning reaction") as though this were a new and unexpected situation. There may be increased reactivity to the next subsequent visual signal, even though it is a "negative" signal.

Table 1.—*CR Results of Normal Subjects**

Name Date (1951)	Verbal Formulation	Hand Movements		Chest Movements	PGR Drop	PGR Drop as Percentage of UR	
		Spontaneous	Integrated			CS −	CS +
J. S. 1/15	D	..	D	..	D	80	117
W. H. 1/16	D	O	D	D	D (?)	22	30
J. G. 1/17	D	..	D	O	D (?)	73	97
B. S. 1/17	D	D	D	U	D	22	59
H. S. 1/23	D	D	D	D	D	26	55
U. M. 1/30	D	D	D	U (?)	D	25	44
D. K. 2/2	D	D	D	O	D	12	17
W. O.	D	O	D	U	..	..	...

* Integrated movements were tested after seven CS + trials alternating with six CS − trials. All other responses were evaluated by intercomparisons of last three CS +, last three CS −, first three CS +, and first three CS − trials. The psychogalvanic response (PGR) drop was measured as the rate of fall for 4.5 seconds, and percentages are based on rate of fall to unconditional stimulus as 100%.

In this table, and in Table 2, O indicates no evidence of conditioning; D, conditioning with differentiation, and U, conditioning without differentiation.

Motor (Hand Movements).—Normal Subjects: All normal subjects developed differentiated conditional responses, i. e., pressing on the switch to the positive conditional stimulus and not pressing to the negative conditional stimulus. Four of the eight normal subjects had also good spontaneous conditional response formation with differentiation, as evidenced by significantly greater spontaneous movement to the conditional stimulus (+), as seen in the tremograph records (Fig. 2).

Patients: No patient showed a successful differentiation, either for the integrated or for the spontaneous movements (Table 2). J. C. (Test 1) and F. S. (Test 2) depressed the switch to the conditional stimuli indiscriminately. E. A. and C. P. showed spontaneous, but undifferentiated, tremor of the electrode hand to the conditional stimuli, as mentioned under orienting reflex, while in the others, owing to the diffuse movements, it could not be noted.

Skin Resistance (Psychogalvanic Reflex).—Normal Subjects: Of the eight subjects, five formed psychogalvanic conditional responses with definite differenti-

ation; two formed positive conditional responses with questionable differentiation. One recording was defective (Figs. 2, 4, and 8).

Patients: Twelve tests were done on the six patients; five of the patients showed no evidence of psychogalvanic conditional response formation. J. C. (paretic) in both tests probably showed a slight differentiated conditional response formation (Figs. 5, 6, 7, and 8).

Respiration.—In a subsequent study, Reese[14] has found that respiratory responses to the signals tend to drop out in later trials, an observation suggesting that these responses are not respiratory conditioning per se but represent emotional reactions, perhaps in the nature of anxious behavior or "questioning reactions," diminishing as the novelty diminishes.

Normal Subjects: Five of the eight normal subjects responded to conditional stimuli by disturbances in the respiratory patterns, and two of these responded differentially to positive conditional stimuli. The most frequent changes were "roughness" of cycle and delayed expiration (Fig. 3).

TABLE 2.—*CR Results with Patients**

Name Date (1951)	Test No.	Verbal Formulation	Hand Movements		Chest Movements	PGR Drop	PGR Drop as Percentage of UR	
			Spontaneous	Integrated			CS −	CS +
E. M. 1/16	2	O	O	O	U	O	18	16
F. S. 2/7	2	O	O	O	O	O	10	5
C. P. 2/7	2	O	U	O	U	O	14	14
J. C. 2/7	2	O	..	O	U (?)	D (?)	32	42
C. W. 2/7	3	O	O	O	U (?)	O	8	5
E. A.	4	O	U	O	U	O (3 previous)	..	..

* As indicated, this is a summary of the second, third, or fourth test. Each patient had two to four times as many trials as did the normal subjects.

Patients: None of the six patients responded differentially to the conditional stimuli. Five probably responded similarly to positive CS and negative CS, but two of these partially obscured respiratory responses by naming color of light with each presentation (Fig. 6).

Verbal Responses.—In brief, all the normal subjects verbalized the significance of each signal without leading questions, and none of the six patients said anything which indicated they had made the crucial connections, despite questions which all but formulated the essence of the test.

COMMENT

In the normal subject, when a mild electric shock is used as the unconditional stimulus, and different colored electric lights are used as conditional signals, there is rapidly developed a motor conditional response with definite psychogalvanic concomitants. The patients with a severe organic psychosis, on the other hand, are unable to form either the psychogalvanic conditional response or the motor condi-

14. Reese, W. G.: Certain Aspects of Conditioning in the Human, Ann. New York Acad. Sc. **56**:330-341, 1953.

tional response,[11] although they show a good psychogalvanic response to the shock itself. Neither patients nor controls showed appreciable change in heart rate during the shock, during the conditional response to the signal for the shock, or during the orienting response.

The change in the psychogalvanic reflex and the complete lack of change in heart rate both in normal subjects and in patients indicate that all autonomic components do not have the same sensitivity. As we have previously obtained marked changes in cardiac rate in the dog in comparable experiments, the data of the present research indicate a marked difference in system sensitivity between dog and man.

Parallel studies of the conscious motor responses and the autonomic responses not only have an advantage for the physiology of slight emotional acts, but the autonomic responses, not being in consciousness, are not so easily inhibited. This fact has been made use of in the so-called lie detector, wherein the autonomic components of a speech response are recorded. The cardiovascular and psychogalvanic responses may give evidence of an emotional disturbance or conflict not revealed verbally. A large number of other comparative studies have been made of subjects under stress (Luria,[15] Malmo and associates,[16]) but none of this work shows the change in relation to circumscribed excitation and inhibition of acquired and inborn responses such as we are able to see by the conditional response methodology.

So far as we are aware, this study is the first of the psychogalvanic response as a feature of the orienting experience. In most subjects we were able to show a definite psychogalvanic response to each new auditory,[17] tactile, or visual stimulus.

Burch and Ray, at Tulane University of Louisiana, have recently shown that there is a cardiovascular component of the orienting response in the human being. They have demonstrated with plethysmographic records that there is a brief, but definite, alteration in the volume of the finger to novel stimuli of various sorts. Their responses are extinguished by several repetitions, show spontaneous restoration on the next day, and have other characteristics of orienting behavior (unpublished data furnished in January, 1953).

SUMMARY AND CONCLUSONS

Patients with cerebral damage show striking inability to learn conditional responses, which normal subjects learn regularly and promptly.

The patients, who had severe, diffuse cortical impairment, uniformly failed (within 6 to 23 reinforced stimulations) to establish discriminative conditional

15. Luria, R. A.: Nature of Human Conflicts or Emotions: Conflict and Will, translated from the Russian and edited by W. H. Gantt, New York, Horace Liveright, Inc., 1932.

16. Malmo, R. B.: Experimental Studies of Mental Patients Under Stress: Feelings and Emotions, New York, McGraw-Hill Book Company, Inc., 1950.

17. We originally used auditory stimuli—tones—for the conditional stimuli, but as these produced in some subjects a large psychogalvanic component, which was often difficult to extinguish, we later substituted for the auditory stimuli visual signals, which had a smaller psychogalvanic component. Welch (Welch, L.: Human Conditioning and Anxiety, Ann. New York Acad. Sc. **56**:*266-272*, 1953) found that anxious patients gave a more pronounced psychogalvanic response to auditory stimuli than do normal subjects, and that this psychogalvanic response is more difficult to extinguish than it is in the normal. Welch was evidently working with the orienting reflex (questioning reaction) produced by the auditory stimuli. This is corroborated by our work showing that the motor component of the OR is exaggerated in both excitable dogs and in anxiety patients.

responses to visual stimuli associated with a slightly painful electrical stimulus. The types of reaction which were recorded include skin resistance, respiratory movements, heart rate, spontaneous and integrated motor movements (tremors and gross movements), and verbal formulation. In none of these forms of behavior did the brain-damaged patients show any formation of conditional responses. This is in marked contrast to responses of the normal subjects, who, after two to seven reinforcements, invariably showed evidence of conditioning. In the normal, the evidence of conditional response formation was always present with integrated motor responses and in verbal formulation, and usually in the psychogalvanic reflex.

In the human subject, changes in heart rate in relation to conditional reflex formation are much less marked than in comparable experiments on dogs. Clarification of this difference awaits more refined study.

APPENDIX

PATIENT J. C.—*Diagnosis: Tertiary syphilis, meningoencephalitis, and generalized arteriosclerosis.*

A Negro aged 57 was admitted to Veterans Administration Hospital, Perry Point, Md. Oct. 3, 1950, with the diagnosis of dementia paralytica. No accurate history of his syphilitic infection is known, but he was apparently working until a few weeks prior to admission. On admission he was disoriented, confused, perserverating, incoherent, and euphoric. The Kahn reaction of the blood was 4+. Spinal fluid studies revealed a 4+ reaction to the Kolmer test; 137 cells per cubic millimeter, with 90% monocytes, and 87 mg. of protein per 100 cc., and a 555543211 colloidal gold curve. Treatment with 9,000,000 units of penicillin on Oct. 5 to 19 resulted in slight clinical improvement.

The patient was tested in the laboratory on Oct. 17, 1950, and Feb. 7, 1951. On the latter date there was an improvement in the clinical picture; he was approximately oriented to time and place, less confused, and more alert. His initial mental status revealed euphoria, confusion, perseveration, marked memory loss for recent events, no immediate recall, inability to remember three things, being able to remember only five digits forward and none backward, and misunderstanding and misinterpretion of instructions. Physical examination showed general and cerebral arteriosclerosis, saber-like shins, and pronounced clumsiness in fine movements. Neurological examination showed small, slightly irregular pupils, which reacted to light and in accommodation; arteriosclerotic vessels in the fundi; generalized insensitivity to pinprick and light touch; equal and active deep reflexes on the two sides; absence of radial and ankle jerks; a negative Romberg sign, and absence of pathological toe signs. In the original test, he was able to identify verbally the two conditional stimuli but was unable to integrate or condition on a motor level. He understood the instructions but did not carry them out correctly.

PATIENT F. S.—*Diagnosis: Marked cerebral arteriosclerosis, with psychotic reaction; convulsions; alcoholism, and intellectual impairment.*

A white man aged 53, who had been a laborer and a truck driver for years, had a long history of heavy drinking and hospitalizations for injuries sustained while drunk and of two hospitalizations in 1945 for delirium tremens. From 1945 to 1950 he had convulsions associated with drinking. In 1948 the diagnosis of arteriosclerosis was made from clinical findings and an abnormal electroencephalogram. The circumstances leading to the present hospitalization (Oct. 13, 1950) were drinking and a hallucinatory experience, in which he severely slashed his throat on Oct. 10. He was tested in our laboratory on Nov. 21, 1951, and Feb. 1, 1951.

The patient was a slovenly man, looking older than the asserted age of 53. He was oriented for time, place, and person and was pleasant and cooperative. Superficial examination revealed no gross impairment of memory, but careful questioning brought out a marked deficit from 1920 to 1930; after 1930 the memory was better, but was still very poor. His memory for recent events seemed fairly good: he could repeat five digits forward and three backward, remembered three things fairly well but with distortion, and was unable to do the 100–7 test or simple calculations.

Physical examination showed generalized arteriosclerosis. The eyegrounds showed narrowing and arteriovenous nicking of the arteries and pale discs. Neurological examination revealed a broad-based gait, good coordination, a stocking-and-glove type of diminished sensation to pinprick and light touch to the midarm and midcalf; the deep reflexes diminished peripherally with absence of the ankle and knee jerks on the right; the Romberg sign was negative; there were no pathological reflexes. The electroencephalogram showed abnormally fast activity with spike seizure activity, which pointed to generalized cortical damage. Routine tests, including examination of the spinal fluid, were within normal limits. During the CR test he was unable to integrate the stimuli and did not differentiate or form conditional responses.

PATIENT E. A.—*Diagnosis: Korsakoff's psychosis.*

A white man aged 55, married, had a record of alcoholism (beer and wine) from 1920 to 1950. A steel worker from 1920 to 1937, he was unemployed from 1937 to 1950. He was admitted to the Veterans Administration Hospital, Aspinwall, Pa., on July 30, 1950, because of a drunken stupor, estimated to be of two to three days' duration. On admission, he was in a critical condition for 28 hours with pneumonia, delirium, and intoxication. He recovered slowly and steadily, but it was noticed that he was confused, disoriented, and confabulatory and had difficulty in walking and staying in bed. A diagnosis of Korsakoff's psychosis was then made, and he was transferred to the Veterans Administration Hospital, Perry Point, on Oct. 11, 1950. Tests in our laboratory on Nov. 7, Nov. 11, and Nov. 21, 1950, and on Feb. 8, 1951, showed the same clinical picture on each occasion, viz., a thin, old, weather-beaten, sloppy, white man, who talked in an uncontrolled, slurred, loud voice. Speech was not spontaneous; it was disconnected, confabulatory, rambling, sometimes incoherent, and illogical. The mood was variable, depending upon the tone of the conversation. Unaware of his surroundings, he did not respond to loud noises or activity related to him. There were no hallucinations, delusions, or special preoccupations—only a marked confabulation. He was completely disoriented for time and place. The date changed, but usually it was around 1917 or 1918; and he thought that he was in France in an Army hospital. Memory for recent events was completely lacking, and memory for remote events was colored by confabulation; but he could remember the doctor's name (W. G. R.) for about two minutes, and then had no recollection of it—"never heard your name." He was unable to do simple calculation. Neurological examination revealed slurred voice, gross cerebellar ataxia, a positive Romberg sign, poor coordination in the finger-to-finger and finger-to-nose test, nystagmus (both eyes), deep reflexes equal and active, no clonus, a negative Hoffman sign, plantar reflex downward, and a spotty picture of decreased sensitivity peripherally. The electroencephalogram showed S-1 diffuse cortical damage. Routine laboratory examination revealed nothing abnormal.

PATIENT C. W. *Diagnosis: Psychosis with paranoid delusions and alcoholism.*

A white man aged 38, married, had been a successful businessman before his illness. At Veterans Administration Hospital, on March, 1950, he was treated with insulin coma, and the sixth coma was a prolonged one, lasting three weeks. After he regained consciousness, there were marked memory deficit, gross intellectual impairment, and clouded sensorium, with child-like (nonresponsive) behavior and lethargy. He was transferred to Veterans Administration Hospital, Perry Point, Oct. 11, 1950, for psychiatric care and rehabilitation. When he was tested in our laboratory on Nov. 14, 1950, Dec. 5, 1950, and Feb. 7, 1951, the clinical picture was the same on each occasion, with disorientation for time and occasionally for place. Pleasant, cooperative, apologetic, and apathetic, he was unable to count seven digits forward and none backward and was unable to do 100–7 or simple arithmetical calculations. He showed gross inability to analyze and synthesize incoming sensory stimuli. He was able to distinguish signals but was unable to integrate and perform, always needing the US to produce action. Psychological testing revealed a Wechsler-Bellevue I. Q., full-scale, of 64, gross intellectual impairment, and poor memory. Physical and neurological examinations showed nothing abnormal. The electroencephalogram was interpreted as within normal limits.

PATIENT E. M. M.—*Diagnosis: Korsakoff's psychosis.*

A white man, aged 54, married, had worked as a clerk in a government office until August, 1950, when he was retired because of hypertension and chronic prostatitis. Prior to this time he was known as an odd person who did excessive drinking and had several episodes of delirium tremens. Since August, 1950, he had been drinking more heavily and his personality

had changed; he had become more seclusive, and had paranoid and some grandiose ideas, but the most remarkable change was an amnesia covering the year 1950. He was admitted to the Veterans Administration Hospital, Perry Point, on Jan. 13, 1951, because of difficulty of management at home. At the time of testing in our laboratory (Jan. 16) he was disoriented for time and place and confused. His memory for recent events was very poor. He did not have pertinent information about the last war, saying it was still going on. He tended to confabulate. He recalled seven digits forward, performed 100–7 correctly, but could not remember three things for five minutes. There was no difficulty with test phrases. Physical examination was noncontributory, and the neurological status was within normal limits except for diminished peripheral sensation. During the testing situation he was alert and cooperative and understood instructions. In his formulation he was able to decide upon the proper CS+, but he did not come to this conclusion easily. It is probable that he has retained some simple integrative function.

PATIENT C. P.—*Diagnosis: Arteriosclerosis, cerebral with psychosis.*

A white woman aged 70-80, during her early life had been characterized as a person with psychopathic tendencies. She had worked in numerous Civil Service jobs but had always been discharged because of poor efficiency. The onset of her present illness began in 1942, when she became increasingly seclusive, suspicious, paranoid, and forgetful, until she was committed to the Veterans Administration Hospital, Perry Point, June, 1947. On admission her mental status was characterized by confusion, persecutory ideas, and memory loss for recent events. During her hospitalization her persecutory ideas have diminished, leaving disorientation, confusion, and marked loss of memory for recent and past events to the point of not being able to remember her way around the hospital area. On being tested on Dec. 29, 1950, and Feb. 7, 1951, she showed disorientation, confusion, slight incoherence, and extremely poor memory for recent events on each occasion. She was unable to remember even the broad outlines of the test, giving totally irrelevant answers to simple questions regarding the test. Physical and neurological examinations revealed nothing except a very decrepit old woman who had difficulty in getting around and who was constantly rambling incoherently and irrelevantly. During the test she did not condition, integrate, or differentiate.

Dr. John C. Whitehorn made valued comments on and revisions in this article.

COLD PRESSOR TEST IN FUNCTIONAL PSYCHIATRIC SYNDROMES

WALTER W. IGERSHEIMER, M.D.
NEW HAVEN, CONN.

IN RECENT years much work has accumulated on the physiological reaction patterns of functionally psychotic patients in a state of homeostasis and stress. An excellent summary of this work is contained in Gellhorn's "Physiological Foundations of Neurology and Psychiatry."[1] Under the headings of "Autonomic Reactions in Schizophrenia," "The Endocrines and Autonomic System in Schizophrenia," and "Cortico-Hypothalamic Relations in Schizophrenia," Gellhorn fits this accumulated evidence logically into his theories about the role which autonomic centers in the hypothalamus play in the etiology of the functional psychoses. The gist of Gellhorn's theories is that in the functional psychoses, particularly schizophrenia, there is a deficient reactivity of the sympathetic division of the autonomic nervous system in the hypothalamus. This deficiency may be initiated by overactivity or constitutional factors. It results in decreased blood pressure and lessened circulatory adjustment reactions, as well as in diminished muscle tone, and leads to impaired hypothalamic control of the hypophysis, with resultant endocrine disturbances. Reduced reactivity of the hypothalamus to cortical stimuli leads to further disturbances in homeostasis. Gellhorn postulates that the mental changes in schizophrenia are primarily related to a defective hypothalamic-cortical discharge.

This paper concerns itself particularly with the problem of vascular reactivity as expressed in blood pressure changes in response to sudden immersion of a hand in water at 4 C. That autonomic vascular responses are deficient in schizophrenics was demonstrated by Pfister,[2] who showed that there was a diminished reactivity of the sympathetic centers to changes in posture. The performing of Schneider tests led to similar conclusions.[3] The Worcester group found that schizophrenics, as compared with the normal population, had a relatively low systolic and diastolic blood pressure.[4] Hoskins characterized the schizophrenic as a person with sluggish sympathetic reactivity.[5]

Prof. George F. Mahl gave assistance in the analysis of the results presented in this paper.

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From the Department of Psychiatry, Yale University School of Medicine, and the Connecticut State Hospital, Middletown, Conn.

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In an earlier investigation,[6] it had been observed that schizophrenic and manic-depressive patients had extremely low cold pressor responses. This observation was made on a small patient population and was coincidental to the main purpose of that investigation. To date, little systematic work has been done in comparing critically and rigorously the cold pressor responses of normal persons with those of patients with various functional psychiatric syndromes. However, it would seem, in view of the increasing evidence that the cold pressor response is based on a neurogenic reflex,[7] that this test may prove to be a useful experimental tool in further investigating in the human subject the neurophysiological units which, according to Gellhorn, are implicated in the etiology of the functional psychoses.

In this paper an attempt will therefore be made to determine whether there does or does not exist a difference in the cold pressor response among patients with various psychiatric syndromes. If such a difference is indeed present, this may then serve as a basis for further clinical research.

METHOD

The cold immersion test of Hines and Brown[8] was used as a standard stimulus and was applied to groups of normal subjects and psychoneurotic, schizophrenic, and manic-depressive patients (Table 1). It was easily administered, and a large sample of cold pressor responses in the nonpsychiatric population was available for comparison with the results obtained in this study.[9] Its method of application closely followed that of Hines and Brown and has previously

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(*Footnote continued on next page*)

been described.[6] A group of 15 normal men were subjected to the cold pressor test. In addition, an experienced anesthetist [10] anesthetized them with thiopental sodium, producing clearly defined and progressively deep levels of anesthesia. Cold pressor responses at these various stages of anesthesia were then reobtained, using the same test procedure as before anesthetization (Table 3).

TABLE 1.—*Cold Pressor Responses in Normal, Psychoneurotic, Schizophrenic, and Manic-Depressive Males and Females*

		Normal Group			
Sex		Males		Females	
Subjects, no.		20		17	
		Mean	S. D.	Mean	S. D.
Age, yr.		26.8	.....	28.7	.....
Resting blood pressure	Systolic	120.4	±10.09	116.3	± 9.76
	Diastolic	65.2	±13.08	68.0	± 6.86
Cold pressor response	Systolic	18.2	± 5.94	13.8	± 6.39
	Diastolic	21.8	± 7.18	16.4	± 5.62

		Psychoneurotic Group			
Sex		Males		Females	
Subjects, no.		7		11	
		Mean	S. D.	Mean	S. D.
Age, yr.		37	.....	32	± 6.66
Resting blood pressure	Systolic	124.9	±11.25	115.7	± 8.47
	Diastolic	65.4	±10.24	68.6	±13.05
Cold pressor response	Systolic	14.0	± 9.12	20.9	± 9.45
	Diastolic	16.0	± 9.30	18.6	±11.17

		Schizophrenic Group			
Sex		Males		Females	
Subjects, no.		16		13	
		Mean	S. D.	Mean	S. D.
Age, yr.		30.5	.....	33.5	.....
Resting blood pressure	Systolic	118.3	±15.25	110.7	± 9.53
	Diastolic	65.4	±13.61	65.3	± 7.30
Cold pressor response	Systolic	6.1	± 4.87	6.8	± 6.58
	Diastolic	9.6	± 5.97	8.8	± 5.36

		Manic-Depressive Group			
Sex		Males		Females	
Subjects, no.		2		4	
		Mean	S. D.	Mean	S. D.
Age, yr.		43.5	.....	± 38	±11.68
Resting blood pressure	Systolic	117.5	± 2.50	±122.0	±12.74
	Diastolic	74.0	± 4.00	± 73.5	± 4.39
Cold pressor response	Systolic	5.5	± 0.50	± 6.5	± 1.5
	Diastolic	5.0	± 3.00	± 4.5	± 5.58

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10. Louis J. Hampton, M.D., associate professor in anesthesiology.

No test was included during which obvious reflex motor activity or a marked emotional reaction occurred in response to the stimulus.

All blood pressure readings were taken with the same sphygmomanometer and by the same investigator.

SUBJECTS

All subjects were free from any serious physical illness, particularly those affecting the cardiovascular system. No subjects with resting blood pressures of 145 mm. Hg systolic and 95 mm. Hg diastolic or over were included, since these levels represent possible latent hypertension.[7a] Blood pressure data which might conceivably have been influenced by the administration of drugs or organic therapies were excluded.

1. *Normal Group.*—Although the concept of psychiatric normality is a relative matter in the light of modern psychodynamic theory,[11] for the purpose of this study it is defined as follows: The subjects so labeled did not in their own judgment or in that of others require consultation with a psychiatrist, nor had they received any psychiatric treatment in the past. They were apparently functioning reasonably well and felt reasonably well adjusted. (*a*) Males: Twenty men, ranging in age from 22 to 65, were included, 15 of whom were medical students. (*b*) Females: Seventeen women, ranging in age from 20 to 58, were included, 11 of whom were nurses.

2. *Psychoneurotic Group.*—Under this diagnostic heading a great variety of emotional reaction patterns are included. It is realized that thereby many uncontrolled variables are introduced. However, this group was included since it did represent patients who had either actively sought or been referred for psychiatric care. This was given at the Yale psychiatric inpatient service. All the patients were in the open ward, had going-out privileges, and participated freely in sports, social entertainment, and occupational therapy on and off the grounds. None of them remained invalided in bed. They were visited regularly by their relatives and paid home visits. All were receiving psychotherapy from psychiatric residents.

(*a*) Males: Seven patients, ranging in age from 17 to 43, were included. Their hospital diagnoses were as follows: Four had character neuroses, passive dependent type, marked by alcoholism (2) voyeurism (1), and latent homosexual trends (2). Three had psychoneuroses, mixed forms, including obsessive-compulsive features (2), hypochondriacal fears (1), depressive reaction (1), and phobias (2). Two patients included here were at times thought of as latent schizophrenics.

(*b*) Females: Eleven patients, ranging in age from 20 to 40, were included. Their hospital diagnoses were as follows: Seven had character neuroses, including passive-aggressive reactions (2), aggressive reactions (1), antisocial types (2), delinquency (1), hysterical character (2), and paranoid trends (2). Four had psychoneuroses, mixed type, marked by obsessive features (3), compulsions (1), depressive features (1), and hysterical features (3). Four patients included here were at times thought of as latent schizophrenics.

3. *The Schizophrenic Group.*—Under this heading are included all those patients who received the diagnosis of schizophrenia (of whatever type) after prolonged study. Again, one could claim that what is called schizophrenia may eventually be separated into distinct and different entities. For the present, however, the official hospital diagnosis will have to suffice. Of 29 schizophrenic patients, 19 were in the closed wards of the Connecticut State Hospital. With most of the patients at the Yale psychiatric inpatient clinic, an active attempt at individual psychotherapy was made by psychiatric residents, while the patients at the Connecticut State Hospital received individual attention and therapy when this was possible. Both groups participated in occupational therapy, for which there was more opportunity at the state hospital. Their relatives visited them occasionally, and on a few occasions patients were allowed to visit their homes. Whenever possible, they were given an opportunity to join patients in the open ward, to take part in sports and social entertainments, and to have ground privileges.

(*a*) Males: Sixteen patients, ranging in age from 19 to 54, were included. Their discharge diagnoses were as follows: paranoid type (14); catatonic type (1); simple type (1).

(*b*) Females: Thirteen patients, ranging in age from 19 to 58, were included. Their hospital diagnoses were as follows: paranoid type (11); catatonic type (2).

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4. *The Manic-Depressive Group.*—Under this heading are included all those patients who were given the diagnosis of manic-depressive psychosis, of whatever type, after prolonged study. Once, again, the difficulty of psychiatric diagnosis presents itself. What has been called a psychosis of this type might have been designated as of a different type by another hospital. For the present, however, the official hospital diagnosis will have to suffice. Of six patients with manic-depressive psychosis, three were patients in the closed ward of the Yale psychiatric clinic, and three were patients in the closed wards of the Connecticut State Hospital. With most of the patients at the Yale psychiatric inpatient clinic, an attempt at individual psychotherapy was made by psychiatric residents, while the patients at the Connecticut State Hospital received individual attention and therapy when this was possible. Both groups participated in occupational therapy, for which there was more opportunity at the state hospital. However, since four of the six patients were very depressed, their participation was minimal. Their relatives were encouraged to visit, and on a few occasions the patients were allowed to visit their homes. Whenever possible, they were given an opportunity to join patients in the open wards, to take part in sports and social entertainment and to have ground privileges.

(*a*) Males: Two patients, ranging in age from 30 to 57, were included. Their hospital diagnoses were as follows: manic type (1); depressed type (1).

(*b*) Females: Four patients, ranging in age from 20 to 60, were included. Their hospital diagnoses were as follows: manic type (1); cyclic type (1), depressed type (2).

RESULTS

In order to make comparisons of cold pressor responses in the groups of normal, psychoneurotic, schizophrenic, and manic-depressive subjects, it was first necessary to test for the significance of the age and sex variables.

1. *Age Variable.*—The entire male and female experimental population was divided into age periods of 10 years, starting with 20 and ending with 59. The males and females were distributed separately, as were the systolic and diastolic cold pressor responses. The median cold pressor response for each age period was then obtained.

When the median systolic and diastolic cold pressor responses were compared for the various age periods in both the male and the female subjects, no progressive trend in any direction could be ascertained.

It seems justified, therefore, to conclude that age was not a significant variable in the results obtained with this sample. Therefore, the age factor is not controlled in the following analysis.

2. *Sex Variable.*—The variances and the means of the systolic and diastolic cold pressor responses of the males were compared with those of the females. This was done separately for each diagnostic group.

There was no significant sex difference in the systolic and diastolic cold pressor responses within the psychoneurotic, schizophrenic, or manic-depressive group. In the normal group, however, the systolic and diastolic responses in the males were significantly more variable than in the females (t test, $P < 0.01$). Allowing for this difference in variability, the mean response for males was also significantly greater than that of the females (t test, $P < 0.05$).

From these results, it was concluded that a sex variable could significantly distort the intergroup comparison. Therefore, the results in all the groups were treated separately for males and females.

3. *Diagnostic Group Differences in Cold Pressor Responses.*—Pertinent data are summarized in Table 1. The analysis of variance showed that there was a

significant diagnostic group difference for both the systolic and the diastolic cold pressor responses. In both males and females the variance attributable to diagnostic groups was significant at less than the 1% level ($P < 0.01$).

Individual intergroup comparisons of mean responses were made with the t test. The results are summarized in Table 2.

TABLE 2.—*T-Test for Reliability of Magnitude of Intergroup Differences in Systolic and Diastolic Cold Pressor Responses of Males and Females in Normal, Psychoneurotic, Schizophrenic, and Manic-Depressive Groups*

	Cold Pressor Response			
	Males		Females	
Groups Compared	Systolic	Diastolic	Systolic	Diastolic
Normal vs. psychoneurotic	No sig. diff.	No sig. diff.	No sig. diff.	No sig. diff.
Normal vs. schizophrenic	P 0.01	P 0.01	P 0.01	P 0.001
Normal vs. manic-depressive	P 0.01	P 0.01	P 0.02	P 0.001
Psychoneurotic vs. schizophrenic	P 0.04	P 0.07	P 0.01	P 0.001
Psychoneurotic vs. manic-depressive	P 0.04	P 0.05	P 0.01	P 0.001
Schizophrenic vs. manic-depressive	No sig. diff.	No sig. diff.	No sig. diff.	No sig. diff.

TABLE 3.—*Summary of Cold Pressor Responses of Fifteen Normal Males in Various Stages of Anesthesia*

Depth of anesthesia		Stage II: II-III: Plane 1		Stage III: Plane 1		Stage III: Planes 1-2 and 2	
Subject, no.		4		5		6	
		Mean	S. D.	Mean	S. D.	Mean	S. D.
Preanesthetic resting blood pressure	Systolic	118.5	2.50	122.4	9.16	121.3	10.61
	Diastolic	70.0	6.12	65.8	18.68	66.2	4.63
Preanesthetic resting cold pressor response	Systolic	21.5	6.00	21.6	5.12	14.0	4.65
	Diastolic	31.8	6.49	21.6	5.39	19.2	5.84
Anesthetic resting blood pressure	Systolic	119.5	8.64	114.0	12.84	120.0	11.15
	Diastolic	73.5	2.18	74.0	12.13	71.7	11.64
Anesthetic cold pressor response	Systolic	16.5	5.54	11.6	3.88	4.0	2.24
	Diastolic	24.5	5.36	12.4	1.50	7.3	1.60
% CPR * decrement with subject under anesthesia	Systolic	—23.3	.....	—46.3	.....	—71.3	.....
	Diastolic	—23.0	.....	—42.7	.....	—62.8	.....

* Cold pressor response.

From Tables 1 and 2 it is evident that there is not a significant difference between the systolic and the diastolic cold pressor responses in males and females when normal subjects are compared with psychoneurotic patients, and when schizophrenic are compared with manic-depressive patients.

There is a significant difference between the systolic and the diastolic cold pressor response in the males when psychoneurotic patients are compared with manic-depressive and schizophrenic patients.

There is a highly significant difference between the systolic and the diastolic cold pressor responses in the males and in the females when the normal subjects are compared with the schizophrenic and manic-depressive patients and when the psychoneurotic females are compared with the manic-depressive and schizophrenic females.

4. *Effect of Increasing Depth of Thiopental Sodium Anesthesia on the Cold Pressor Responses of Fifteen Normal Males.*—In Table 3 are shown the results of performing the systolic and diastolic cold pressor tests in a group of normal men in various depths of thiopental sodium anesthesia. From these data it appears that with increasing depths of anesthesia there is an increasing percentage decrement in the systolic and diastolic cold pressor responses.

COMMENT

The most striking result of this investigation is the significantly lower cold pressor response in the schizophrenic than in the normal subjects. There were five patients in the entire schizophrenic group who had no cold pressor response or who had a paradoxical response (a slight lowering of the blood pressure). Among manic-depressive patients there was one paradoxical response, while no such response was found among the normal and psychoneurotic groups.

The manic-depressive group was too small to permit an adequate deduction of significant facts. However, these patients showed a trend similar to the schizophrenic group.

The cold pressor responses of the psychoneurotic group resembled those of the normal group. However, the cold pressor responses showed a greater range and variability and the mean group responses tended to be lower than those of the normal group, although this difference was not statistically significant. Since in this category is included a wide spectrum of psychiatric syndromes, and since the lowest reactors in this group were the patients whose illness was diagnosed as possible borderline schizophrenia, one wonders whether this group does not occupy an intermediate range with regard to the cold pressor response between the normal and the psychotic group.

These results seem to fit very well indeed in considering the findings and theories of the above-cited investigators.[12] In general, they point to a markedly diminished vascular reactivity in the functional psychoses, with the possibility that the psychoneurotic group may exhibit an increased vascular lability and an over-all intermediate position between the vascular reactivity of the normal and that of the psychotic groups. From the results presented, it is not possible to localize a site of autonomic imbalance in terms of Gellhorn's deficient reactivity of the sympathetic division of the hypothalamic autonomic centers. On the other hand, two findings in this study seem to lend particular support to his theories.

1. In a group of 15 normal medical students under anesthesia at Stage II and Stage II-III, Plane 1 (in which surgical anesthesia is achieved and cortical reactivity to cold stimulation excluded) there was only a 23% decrement in the systolic and diastolic cold pressor responses. This result suggests that subcortical autonomic centers were implicated in the cold pressor responses. The increasing decrement in the cold pressor responses with increasing depth of anesthesia (Stage III, Planes 1 and 2) merely points to the fact that the cold pressor response closely parallels the physiology of a neurogenic reflex. It does not, however, permit exact localization of the autonomic centers involved.

12. Gellhorn,[1] Pfister,[2] Linton, Hamelink, and Hoskins,[3] Freeman, Hoskins, and Sleeper,[4] Hoskins and Jellinek,[5] Hoskins.[5]

2. Mention has been made of the fact that "paradoxical" cold pressor responses were observed in some schizophrenic patients. Similar observations were made by Reider.[13] Such "paradoxical" responses to cold stimulation suggest marked hyporeactivity, or even temporary functional paralysis, of the sympathetic centers, while concomitantly the vagal-parasympathetic centers may be hyperreactive. Such a response is more easily accounted for by assuming central, rather than peripheral, dysfunction. Moreover, the studies of Bronk and associates [7,8] suggest the possibility that the hypothalamus can exert an inhibitory or a depressor effect on the vasomotor-regulating centers in the brain stem. This effect results when the hypothalamus discharges specifically slow electric impulses. The "paradoxical" cold pressor response, and, indeed, the low cold pressor responses, in the schizophrenic and manic-depressive groups may thus be under the over-all influence of a hypothalamic depressor mechanism governing lower autonomic centers.

It is suggested that the cold pressor test is useful in studying reactivity of the autonomic nervous system in functional psychiatric syndromes, and that it may in time contribute to the localization of the autonomic centers which appear to be impaired, particularly in the functional psychoses.

SUMMARY AND CONCLUSIONS

An intergroup comparison of normal, psychoneurotic, schizophrenic, and manic-depressive subjects using the cold pressor test of Hines and Brown was made.

Statistically significant differences were observed between the normal and the schizophrenic group (both males and females) and between the females of the psychoneurotic and schizophrenic groups. A similar trend was observed when the normal group and the psychoneurotic group were compared with the manic-depressive group, although the latter was too small for adequate statistical analysis.

The group of psychoneurotic patients seemed to occupy an intermediate position between the normal and the psychotic group with regard to the cold pressor responses.

The significantly lower cold pressor responses in the schizophrenic and manic-depressive subjects were related to Gellhorn's theory of deficient reactivity of the sympathetic division of the hypothalamus in the functional psychoses, particularly in schizophrenia. A hypothalamic depressor mechanism governing lower vasomotor centers is suggested.

"Paradoxical" cold pressor responses found in five schizophrenic subjects were interpreted according to Gellhorn's theories, emphasizing that the vagal-parasympathetic centers may be unusually hyperreactive to cold stimulation in these subjects. Allusion is made to the possibility that this response may be due largely to a depressor effect exerted by the hypothalamus over lower vasomotor centers.

Cold pressor responses in a group of 15 normal subjects under various depths of anesthesia seem to indicate that subcortical autonomic centers are activated by this test, and that it evokes a neurogenic reflex. Specific localization of the activated autonomic centers must await further research.

13. Reider, N.: Blood Pressure Studies on Psychiatric Patients, Bull. Menninger Clin. **2**:65, 1938.

EOSINOPHILE RESPONSE IN SCHIZOPHRENIC PATIENTS

Influence of the Diurnal Cycle and the Type of Schizophrenia

J. A. F. STEVENSON, M.D.
E. V. METCALFE, M.D.
AND
G. E. HOBBS, M.D.
LONDON, ONT., CANADA

THE RECENT advances in the measurement and understanding of endocrine and nervous mechanisms have given impetus to the search for organic physiological causes or correlates in the psychoses. Pincus, Hoagland, and their colleagues [1] have presented evidence from their impressive studies that dysfunction of the adrenal cortex may play an important role in the genesis or development of schizophrenia. The complex mechanisms involved in the regulation and maintenance of body temperature have been found by Buck, Carscallen, and Hobbs [2] to be disorganized in early schizophrenia.

Pincus and associates [1] reported that in schizophrenia there is an absence or a decrease in the adrenocortical response to stimulation. As those schizophrenics who did not show an adequate adrenocortical response to stress did not show one to corticotropin (ACTH) either, they deduced that the defect lay in the adrenal cortex itself. They later presented evidence [3] that in schizophrenia a poor response to a test dose of corticotropin indicated less chance of improvement with electroshock therapy. Hemphill and Reiss,[4] Faurbye and associates,[5] and others have also

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Miss K. Ronni, B.A., was responsible for all of the eosinophile counts and much of the tabulation and statistical work in this study. Mr. D. Pulham was responsible for photography of graphs.

From the Psychiatric Institute, Westminster Hospital (Department of Veterans Affairs); and the Departments of Physiology, and of Psychiatry and Preventive Medicine, University of Western Ontario.

1. Pincus, G., and Hoagland, H.: Adrenal Cortical Responses to Stress in Normal Men and in Those with Personality Disorders: Some Stress Responses in Normal and Psychotic Subjects, Am. J. Psychiat. **106**:641, 1950.

2. Buck, C. W.; Carscallen, H. B., and Hobbs, G. E.: Temperature Regulation in Schizophrenia: Comparison of Schizophrenic and Normal Subjects; Analysis by Duration of Psychosis, Arch. Neurol. & Psychiat. **64**:828, 1950.

3. Hoagland, H.; Callaway, E.; Elmadjian, F., and Pincus, G.: Adrenal Cortical Responsivity of Psychotic Patients in Relation to Electroshock Treatments, Psychosom. Med. **12**:73, 1950.

4. Hemphill, R. E., and Reiss, M.: Experimental Investigations in the Endocrinology of Schizophrenia, Proc. Roy. Soc. Med. **41**:533, 1948.

(Footnotes continued on next page)

reported that some schizophrenics show a deficient adrenocortical response to stimulation.

In apparent disagreement with these observations are those of Stein, Ronzoni, and Gildea,[6] who found no significant difference between the adrenocortical response of schizophrenic and normal subjects to a test dose of corticotropin or to heat stress. Altschule, Promisel, Parkhurst, and Grunebaum [7] also failed to discover any difference, and, similarly, negative results have been reported by others.[8]

Although Pincus and his colleagues used several indices of adrenocortical activity in their studies, many of those who have found no difference between schizophrenic and normal persons relied upon the eosinopenic response [9] as their sole criterion of adrenocortical activity, and the reliability of this has been questioned.[10] The diurnal rhythm in the level of circulating eosinophiles which has been demonstrated by several workers [11] is, however, the reciprocal of that described for the secretory activity of the adrenal cortex.[12] The highest level is reached between midnight and 6 a. m.; a rapid fall occurs about 8 a. m., or the time of rising, and the low point is reached at noon, to be followed by a steady rise to maximum. This diurnal rhythm in eosinophiles is not present in Addison's disease.[11b] Although factors other than adrenocortical activity may effect sudden shifts in eosinophile

5. Faurbye, A.; Vestergaard, P.; Kobbernagel, F., and Nielsen, A.: Adrenal Cortical Function in Chronic Schizophrenia (Stress, Adrenaline-Test, ACTH-Test), Acta endocrinol. **8**:215, 1951.

6. Stein, M.; Ronzoni, E., and Gildea, E. F.: Physiological Responses to Heat Stress and ACTH of Normal and Schizophrenic Subjects, Am. J. Psychiat. **108**:450, 1951.

7. Altschule, M. D.; Promisel, E.; Parkhurst, B. H., and Grunebaum, H.: Effects of ACTH in Patients with Mental Disease, Arch. Neurol. & Psychiat. **64**:641, 1950.

8. Hiatt, H. H.; Rothwell, W. S., and Horwitt, M. K.: Eosinopenia Produced by ACTH in Patients with Schizophrenia, Proc. Soc. Exper. Biol. & Med. **79**:707, 1952.

9. Thorn, G. W.; Forsham, P. H.; Prunty, F. T. G., and Hills, A. G.: A Test for Adrenal Cortical Insufficiency: The Response to Pituitary Adrenocorticotropic Hormone, J. A. M. A. **137**:1005, 1948.

10. Hoagland, H.; Pincus, G.; Elmadjian, F.; Romanoff, L.; Freeman, H.; Hope, J.; Ballan, J.; Berkeley, A., and Carlo, J.: Study of Adrenocortical Physiology in Normal and Schizophrenic Men, A. M. A. Arch. Neurol. & Psychiat. **69**:470, 1953.

11. (*a*) Rud, F.: The Eosinophil Count in Health and Mental Disease: A Biometrical Study, Acta psychiat. et neurol., Supp. 40, 1947. (*b*) Halberg, F.; Visscher, M. D.; Flink, E. B.; Beige, K., and Bock, F.: Diurnal Rhythmic Changes in Blood Eosinophil Levels in Health and in Certain Diseases, Journal-Lancet **71**:312, 1951. (*c*) Stevenson, J. A. F.; Goddard, E. S., and Hobbs, G. E.: Diurnal Variations in Body Temperature and Blood Eosinophil Level in Non-Psychotic and Psychotic Humans, Proceedings of the Canadian Physiological Society, 15th Annual Meeting, 1951, abstracted, Rev. Canad. Biol. **11**:84, 1952.

12. Pincus, G.: Diurnal Rhythm in the Excretion of the Urinary Ketosteroids by Young Men, J. Clin. Endocrinol. **3**:195, 1943. Elmadjian, F., and Pincus, G.: A Study of the Diurnal Variations in Circulating Lymphocytes in Normal and Psychotic Subjects, ibid. **6**:287, 1946. Pincus, G.; Romanoff, L. P., and Carlo, J.: A Diurnal Rhythm in the Excretion of Neutral Reducing Lipids by Man and Its Relation to the 17-Ketosteroid Rhythm, ibid. **8**:221, 1948.

level even upon the administration of epinephrine, it is most likely that any effect produced by corticotropin is mediated through the adrenal cortex.

We found no difference in the character of the diurnal eosinophile cycle between normal controls and a group of randomly selected chronic schizophrenics [13] whose mean age was 42 and whose mean duration of illness was 15 years.

This would confirm the opinion that adrenocortical function in the schizophrenic is not seriously impaired; however, this same group of schizophrenics also showed diurnal cycles of body temperature within the normal pattern and range. These chronic schizophrenics demonstrated essentially normal behavior in these two important indices of diurnal body metabolism. This was not unexpected, however, as Buck, Carscallen, and Hobbs [2] had earlier found that, although an abnormal temperature regulation was characteristic of early acute schizophrenia, a fairly normal diurnal rhythm and response were present in most cases of long duration. More recently Hoagland and associates [10] have reported evidence of some recovery of adrenocortical responsivity to corticotropin in older, more chronic patients.

The present study deals with the acute response in the level of circulating eosinophiles of chronic schizophrenics to the administration of test doses of epinephrine and corticotropin, and in comparable control periods. It was considered that, in conjunction with the corticotropin tests, epinephrine tests should give some evidence of the reactivity of the adrenocortical system.[14] Corticotropin was used to determine the reactivity of the adrenal cortex itself.[9] Determination of the integrated reactivity of the nervous system, anterior pituitary, and adrenal cortex to psychological stress, other than that produced by the procedure itself, was, unfortunately, not feasible, nor were our efforts to obtain a group of normal controls for the epinephrine and corticotropin tests.

PROCEDURE

Thirty male patients were randomly chosen from those classified as schizophrenic by the hospital diagnostic conferences. Their mean age was 34.7 (28 to 42) years, and the mean duration of their illness in hospital was 8.5 (2 to 14) years.

The blood eosinophile level was determined by pricking the finger, drawing the blood into a standard white blood cell pipette to the 0.5 mark, and diluting this to the 11.0 mark with a solution composed of 5 cc. of 2% aqueous eosin and 5 cc. of acetone, diluted to 100 cc. with distilled water.[9] The pipettes were then immediately shaken for one minute on an automatic shaker. Two pipettes were drawn for each observation, and from each pipette two individual Levy (3.2 cu. mm.) chambers were filled and counted; the final count was, thus, the average of four chambers. The count was made as soon as possible after blood letting. The finger punctured was that offered by the subject, for in the case of psychotic subjects it was found that any attempt to use a set sequence met with resistance. An effort was made to have the usual daily routine disturbed as little as possible; meals were served at the regular times.

For the morning studies, blood samples were taken at 8, 9, 10, 11, and 12 a. m., and for the afternoon studies, at 1, 2, 3, 4, and 5 p. m. On the appropriate days 0.3 ml. of epinephrine hydrochloride, 1:1,000, subcutaneously, or 25 mg. of corticotropin, intramuscularly, was administered immediately after the 8 a. m. or the 1 p. m. count. The morning and afternoon series were separated by a week or more for each patient.

13. Hobbs, G. E.; Goddard, E. S., and Stevenson, J. A. F.: The Diurnal Cycle in Blood Eosinophils and Body Temperature, to be published.

14. Recant, L.; Hume, D. M.; Forsham, P. H., and Thorn, G. W.: Studies on the Effect of Epinephrine on the Pituitary-Adrenocortical System, J. Clin. Endocrinol. **10**:187, 1950.

The results have been treated statistically; the significance of differences has been determined for quantitative data by the Student's t test and for enumeration data from fourfold contingency tables.[15] The relative change at any time from the first count of a test has been calculated as the percentage deviation from that first count.

RESULTS

The mean absolute levels of circulating eosinophiles for the group as a whole in the three morning and the three afternoon tests are shown in Table 1. The mean relative changes in these tests are shown in chart 1*A*; as these are the means of the relative changes calculated for each individual subject, they do not agree precisely in every instance with those which can be derived from the data in Table 1.

In view of the marked difference in the spontaneous direction of the morning and afternoon eosinophile changes apparent in the studies of diurnal variation and, again, in the control tests of this study, the epinephrine and corticotropin effects have also been "corrected" for the spontaneous change. These "corrected" mean

TABLE 1.—*Mean Absolute Levels* of Circulating Eosinophiles in Control Periods and Following Administration of Epinephrine or Corticotropin*

	Control	Epinephrine	Corticotropin
Morning			
8 a. m.	287 ± 39.5	268 ± 37.6	269 ± 36.5
9 a. m.	236 ± 34.0	231 ± 34.5	224 ± 32.1
10 a. m.	202 ± 31.2	135 ± 22.0	174 ± 27.4
11 a. m.	218 ± 37.5	146 ± 25.6	144 ± 22.1
12 Noon	227 ± 36.7	150 ± 22.9	138 ± 22.6
Afternoon			
1 p. m.	247 ± 33.0	265 ± 34.1	254 ± 34.9
2 p. m.	230 ± 30.0	256 ± 36.8	223 ± 30.2
3 p. m.	244 ± 33.0	198 ± 28.7	200 ± 29.1
4 p. m.	263 ± 37.7	200 ± 29.5	188 ± 29.3
5 p. m.	308 ± 44.2	238 ± 32.8	192 ± 29.8

* Mean (S. E. M.) absolute levels of circulating eosinophiles for 30 male schizophrenics in control periods and following administration of epinephrine or corticotropin. The epinephrine, 0.3 mg. given subcutaneously, or the corticotropin, 25 mg. given intramuscularly, was administered just after the 8 a. m. or the 1 p. m. count. The morning and afternoon tests were separated by several days for each subject.

relative changes, the differences from the comparable spontaneous, or control, values, are graphed in Chart 1*B*; they may be compared with the uncorrected values shown in Chart 1*A* to demonstrate the effect of the spontaneous cycle on the observed response.

When tests on 20 schizophrenic patients had been completed, the study was considered finished and statistical analysis of the results was begun.[16] The subcategory of schizophrenia in which the patient had been placed at hospital diagnostic conference had been routinely recorded. It was noticed that the paranoid subgroup showed relatively little fall on the control morning; this was found to be significantly

15. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, Ed. 4, Ames, Iowa, The Collegiate Press, Inc., 1946. Mainland, D.: Statistical Methods in Medical Research: 1. Qualitative Statistics (Enumeration Data), Canad. J. Research, Sect. E, **26**:1, 1948.

16. Stevenson, J. A. F.; Hobbs, G. E., and Metcalfe, E. V.: Effect of Diurnal Variation in Level of Circulating Eosinophils on Their Acute Response to Exogenous Adrenalin and ACTH Proceedings of the Canadian Physiological Society, 16th Annual Meeting, 1952, p. 64; Rev. Canad. Biol., to be published.

less than that shown by the other large subgroup, the catatonic. In view of this surprising and unexpected finding, the series was enlarged to 30 patients. The psychiatrist selecting the patients and the technician doing the tests knew nothing of the reasons for this increase in the group size, and all diagnoses were obtained from the official records of the hospital. According to these records, the final composition of the group was as follows:

Schizophrenia	No.	Mean Age	Mean Duration of Illness
Catatonic	11	35.9 ± 1.00	9.7 ± 0.57
Paranoid	12	35.2 ± 1.20	7.6 ± 0.86
Simple	5	34.0 ± 1.52	8.2 ± 1.07
Hebephrenic	2	26.5 ± 1.41	8.0 ± 1.00
Total	30		

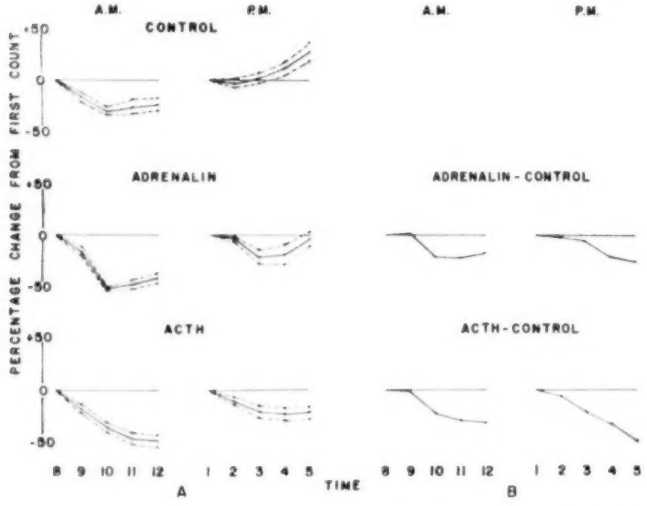

Chart 1.—*A*, mean relative changes in level of circulating eosinophiles in 30 schizophrenics during control periods and following epinephrine, 0.3 mg. given subcutaneously, and corticotropin, 25 mg. given intramuscularly, administered immediately after the first count. The broken lines signify one standard error of the mean.

B, the mean relative changes following injection of epinephrine and corticotropin "corrected" for the probable spontaneous changes occurring simultaneously.

The standard errors are given with the means. The last two subgroups have not been dealt with in detail, owing to their small size.

The mean absolute level of circulating eosinophiles for the catatonic and paranoid subgroups in the various tests appear in Table 2, and the means of the relative changes (calculated individually) are graphed in Chart 2. The mean relative decreases in eosinophiles were significantly greater (P 0.05 — 0.001) for the catatonic than for the paranoid subgroup in all three morning tests. Comparable measurements on nonpsychotic men were not possible except for the control periods. In the latter instance, the group of orderlies (mean age, 39), which had been studied earlier, but by the same personnel and procedure, provided some data for comparison. These are included in Table 2 and Chart 2.

TABLE 2.—*Absolute Changes in Mean Level of Eosinophiles* Following Epinephrine and Corticotropin Administration to Catatonic and Paranoid Schizophrenics*

	Control			Epinephrine		Corticotropin	
	Catatonics	Paranoids	Orderlies	Catatonics	Paranoids	Catatonics	Paranoids
Morning							
8 a. m.	172 ± 23.6	327 ± 61.9	173 ± 28	157 ± 23.3	309 ± 56.1	156 ± 14.1	316 ± 58.6
9 a. m.	141 ± 20.4	276 ± 52.1	154 ± 23	118 ± 21.8	288 ± 50.4	116 ± 16.8	274 ± 50.1
10 a. m.	104 ± 18.0	254 ± 50.6	137 ± 25	62 ± 10.9	174 ± 33.6	77 ± 10.4	207 ± 36.9
11 a. m.	91 ± 16.6	285 ± 51.6	135 ± 23	61 ± 14.7	198 ± 43.6	53 ± 8.8	184 ± 35.7
12 Noon	90 ± 19.2	304 ± 56.1	127 ± 22	70 ± 12.8	203 ± 44.5	44 ± 6.9	187 ± 38.3
Afternoon							
1 p. m.	134 ± 18.2	298 ± 51.4	139 ± 12	122 ± 17.1	363 ± 57.1	130 ± 13.3	314 ± 55.9
2 p. m.	121 ± 11.5	301 ± 55.1	.....	108 ± 12.1	342 ± 60.8	120 ± 12.8	277 ± 45.7
3 p. m.	118 ± 10.4	314 ± 57.6	.....	81 ± 9.5	257 ± 51.4	83 ± 22.0	225 ± 49.0
4 p. m.	131 ± 9.9	340 ± 68.7	189 ± 26	74 ± 8.7	263 ± 47.5	81 ± 10.3	224 ± 41.5
5 p. m.	148 ± 12.9	382 ± 71.0	.....	94 ± 9.6	304 ± 55.1	89 ± 11.7	227 ± 50.1

* Mean (S. E. M.) absolute levels of circulating eosinophiles for 11 catatonic and 12 paranoid schizophrenics in control periods and following administration of epinephrine and corticotropin. The epinephrine, 0.3 mg. given subcutaneously, or the corticotropin, 25 mg. given intramuscularly, was administered just after the 8 a. m. or the 1 p. m. count. Values obtained for 12 healthy orderlies under conditions similar to the control periods are included.

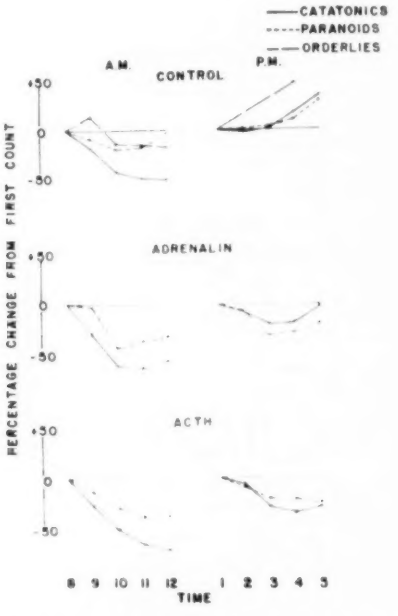

Chart 2.—Mean relative changes in level of circulating eosinophiles in 11 catatonic and 12 paranoid schizophrenics during control periods and following subcutaneous injection of 0.3 mg. of epinephrine hydrochloride and intramuscular administration of 25 mg. of corticotropin immediately after the first count. The values for a group of 12 healthy orderlies, which were obtained under conditions similar to the control periods, are also shown.

The difference between the catatonics and the paranoids is also apparent in the significantly larger proportion of catatonics who showed a fall of 50% or greater in the three morning tests. These results for all persons in all tests are shown in Table 3. The results for both the third and the fourth hours are included to reduce

TABLE 3.—*Individual Responses in Control Periods and Following Epinephrine and Corticotropin* *

Subject		Control		Epinephrine		Corticotropin	
		A. M.	P. M.	A. M.	P. M.	A. M.	P. M.
				Catatonic			
	1	±	—	±	±	±	—
	2	±	..	±	..	±	..
	3	..	..	..	—	..	—
	4	±	..	±	..	±	+
	5	..	..	..	..	±	..
	6	..	..	—	..	+	±
	7	±	..	±	—	±	..
	8	±	..	±	..	±	..
	9	..	—	+	±	±	..
	10	±	..	±	..	±	..
	11	±	..	±	..	±	..
Total	11	7	0	8	2	10	2
				Paranoid			
	12	..	..	..	..	—	..
	13	..	..	..	..	—	..
	14	..	..	..	..	..	..
	15	..	..	+	+	±	..
	16	..	..	..	..	..	+
	17	..	..	—	..	..	±
	18	..	..	..	..	±	..
	19	..	..	..	..	..	—
	20	..	..	..	..	..	..
	21	..	..	..	..	..	+
	22	..	..	..	..	+	..
	23	..	..	±	—	+	+
Total	12	0	0	2	1	4	4
				Simple			
	24	+	..	..	..	+	..
	25	..	..	—	..	..	..
	26	—	..	..	..	..	..
	27	..	..	—	—	..	—
	28	..	..	±	..	+	+
Total	5	1	0	1	0	2	1
				Hebephrenic			
	29	..	..	+	..	±	..
	30	..	..	±	..	±	..
Total	2	0	0	2	0	2	0
Total	30	8	0	13	3	18	7

* Data are on subjects (30 male schizophrenics) showing a drop of 50% or more at the third or the fourth hour. The first count was taken at 8 a. m. or 1 p. m., and epinephrine, 0.3 mg. subcutaneously, or corticotropin, 25 mg. intramuscularly, was administered after this. A 50% or greater decrease by the third hour (11 a. m. or 4 p. m.) is indicated by — and at the fourth hour (noon or 5 p. m.) by +. Totals for the fourth hour only are shown.

any discrepancy due to the speed of response. In comparison, only 2 of the 12 orderlies studied earlier showed a fall of 50% or greater in the morning, as compared with 7 of 11 catatonics and 0 of 12 paranoids on the control morning.

Not only was the degree of relative change of eosinophile level significantly different for catatonics and paranoids in all the morning tests, but the absolute mean

levels of eosinophiles of these two groups were significantly different at all hours in nearly every observation; in the few exceptions the difference approached significance (Table 2). For example, at 8 a. m. on the control morning the mean absolute counts were 175 ± 23.6 for the catatonics and 327 ± 61.9 ($P < 0.05$), for the paranoids, and at 1 p. m. on the control afternoon, 134 ± 18.2 for the catatonics and 298 ± 51.4 ($P < 0.01$) for the paranoids. The stability of the eosinophile level in any group from one day to the next is also apparent; this supports the reliability of the method used to determine the eosinophile count. Comparable data for the healthy orderlies are included. These are similar to those reported by Shands and Bartter [17] for their normal men. It will be noticed that, whereas the catatonics and orderlies have about the same "resting" level of eosinophiles, the paranoids have approximately twice that level.

COMMENT

Schizophrenics as a Group.—Eight of these 30 schizophrenics, or 27%, showed a fall of 50% or more in the level of circulating eosinophiles on the control morning (Table 3). This is somewhat less than the proportion of Rud's [11a] normals, 38%, that Best and Samter [18] calculated showed a drop of 50% or more during the morning period of the daily cycle, but greater than that (2/12 or 17%) observed in our control group of orderlies. Thus, the proportion of this general group of schizophrenics showing a significant spontaneous fall in eosinophiles during the morning hours, presumably the result of adrenocortical activity, is similar to that found among normals.

It is apparent from Chart 1 that both epinephrine and corticotropin cause mean relative decreases greater than those which occur during the corresponding control period. The decreases are significantly greater at the third and fourth hours after administration of either agent, both in the morning and in the afternoon, presumptive evidence of some increase in adrenocortical activity in response to these agents. This fall in number of eosinophiles is, however, not as great as has generally been reported for the response in normal, healthy subjects to similar amounts of epinephrine and corticotropin. Indeed, in the latter instance a fall greater than 50 ± is to be expected in every subject, whereas only 18 of 30 schizophrenics showed such a response to corticotropin in the morning (Table 3). Although these schizophrenics do show evidence of an adrenocortical response to stimulation, it is not as great as normal.

The spontaneous diurnal cycle in eosinophile level previously described is apparent in the morning and afternoon control periods (Fig. 1*A*): The low point is reached about noon and is followed by a gradual rise. The effects of unusual stimulations (corticotropin, epinephrine, etc.) are superimposed on this endogenous cycle, enhancing a decrease and inhibiting an increase. Thus, although the gross effects of epinephrine or corticotropin do not appear to be very great in the afternoon, when the net effects are obtained by "correcting" for the spontaneous change (that shown in the control tests), they are found to be greater, if anything, than the net effect in the morning (Chart 1*B*). Although this needs corroboration in normals,

17. Shands, H. C., and Bartter, Frederic C.: A Statistical Analysis of the "ACTH Test": Changes in the Eosinophil Count in Normal and in Psychoneurotic Subjects, J. Clin. Endocrinol. **12**:178, 1952.

18. Best, W. R., and Samter, M.: Variation and Error in Eosinophil Counts of Blood and Bone Marrow, Blood **6**:61, 1951.

it suggests that the usual criterion of an adequate adrenocortical system in this test—a fall of 50% or greater four hours after administration of epinephrine or corticotropin—may be inappropriate except in the morning, for the relative amount of fall appears to depend upon the coincident direction of the spontaneous diurnal cycle as well as upon the health of the adrenocortical system.

Examination of the individual responses in the various tests (Table 3) reveals a wide variation among patients in the several situations where fairly uniform responses would be expected in a group of normals. This indicates that the diminished response in eosinophile changes, and presumably in adrenocortical activity, shown by this schizophrenic group as a whole may be due to a marked decrease in some schizophrenics only, rather than to a moderate decrease in all schizophrenics, and suggests that types and stages of the schizophrenic syndrome may be associated with different functional states of the adrenal cortex and of the systems regulating it. Evidence for this view appeared unexpectedly in the present study.

Catatonic and Paranoid Schizophrenics.—In the morning studies the group of 11 catatonics approached the normal closely in the "resting" level of eosinophiles (Table 2), in the relative responses to epinephrine and corticotropin (Chart 2), and in the high proportion of the group which showed a fall of 50% or greater four hours after epinephrine (8/11, Table 2) or corticotropin (10/11).

On the other hand, the group of 12 paranoids differed from the catatonics and the normal group in these same indices. The "resting" level approximately twice as high, the mean relative responses to epinephrine and to corticotropin of less than 40%, and the low proportion showing a fall greater than 50% four hours after epinephrine (2/12) or corticotropin (4/12) are presumptive evidence of diminished adrenocortical activity in these paranoid schizophrenics.

The results of the afternoon tests are difficult to interpret, since we lack any observations on the response at this time of healthy controls to epinephrine and corticotropin. The spontaneous direction of the eosinophile level was then upward. This probably accounts for the smaller relative response to epinephrine and corticotropin of the schizophrenics at this time, as compared with that in the morning. As with the general group, if these relative responses are "corrected" for the spontaneous change which would occur at this time of day, both the catatonic and the paranoid groups showed greater mean "corrected" relative responses to epinephrine and corticotropin at this time than in the morning. Such "correction," however, practically removes any difference between the catatonics and the paranoids in both morning and afternoon tests, indicating that the specific additional response to epinephrine or corticotropin may not be very different in the two groups.

The difference between the catatonics and the paranoids is strikingly evident on the control morning. Then, the spontaneous adrenocortical activity apparent in the catatonics was not only much greater than that in the paranoids but was greater than that occurring in normals, certainly than that shown by the group of orderlies; the paranoids showed an essentially normal trend in the relative changes in the eosinophile level.

The term "spontaneous" must by qualified, for Cleghorn and Graham[19] have reported that upon injections of saline patients with anxiety states demonstrated

19. Cleghorn, R. A., and Graham, B. F.: Studies of Adrenal Cortical Activity in Psychoneurotic Subjects, Am. J. Psychiat. **106**:668, 1950.

definite evidence of activation of the adrenal cortex. It may be that pricking the finger is sufficient stress to produce a significant adrenocortical response in the catatonic if this system is already hyperreactive; nevertheless, the difference between the catatonics and the paranoids remains.

The general impression from these observations is that the paranoids show evidence of subnormal activity and response of the adrenocortical system, whereas the catatonics appear to have a moderate hyperactivity, or at least a hyperreactivity, of this system. The reports of Cleghorn [20] and others that paranoid tendencies are not uncommon in Addison's disease and that frank psychoses of a paranoid nature are known to occur in this disease lend support to the hypothesis that adrenocortical hypoactivity is present in many paranoid schizophrenics. On the other hand, hyperreactivity of the adrenocortical system in the catatonics would seem compatible with the more labile nature of their general behavior.

The mean age and duration of illness were almost the same for the catatonics and the paranoids and, therefore, are unlikely to be factors in producing the different behavior of the two groups.

Our results support the contention of Pincus, Hoagland, and their colleagues that dysfunction of the adrenal cortex itself is present in a significant proportion of schizophrenics. They further indicate that hypoactivity and hyporesponsivity may occur frequently in paranoid, but rarely in catatonic, schizophrenics.

These differences between catatonic and paranoid schizophrenics which we have observed may account for the conflicting reports which have appeared on adrenocortical activity in schizophrenia; a group made up largely of catatonics would probably show normal behavior in this regard, whereas one predominantly composed of paranoids would lead to the conclusion that this system was significantly impaired.

In many organic indices schizophrenics have been shown to differ from normal in the range or variability, rather than in the means, of the sample populations. This may be due in some instances to a condition similar to that which appeared in the present study, in which the wide variability of the whole group was in large part due to the inclusion of two relatively distinct subgroups, one similar to, the other significantly different from, the normal.

We are aware of the general vagueness of definition of these diagnostic subgroups. The diagnostic division which occurred in this study and gave such significant separation of eosinophile behavior, and presumably adrenocortical function, may be dependent upon the particular understanding and use of these diagnoses by the psychiatrists who originally classified these patients. Too few cases of the simple and hebephrenic categories appeared in this random series to provide adequate data for analysis and discussion.

SUMMARY AND CONCLUSION

The changes in level of circulating eosinophiles in both morning and afternoon control periods and in response to epinephrine (0.3 mg. given subcutaneously) and to corticotropin (25 mg., intramuscularly) were determined in 30 men hospitalized for schizophrenia an average of 8.5 years.

20. Cleghorn, R. A.: Adrenal Cortical Insufficiency: Psychological and Neurological Observations, Canad. M. A. J. **65**:449, 1951; The Interaction of Physiological and Psychological Processes in Adaptation, Psychiat. Quart. **26**:1, 1952.

The mean changes in eosinophile level observed in the control periods reflect the diurnal cycle of eosinophile level previously described. The mean relative decreases in eosinophiles following administration of epinephrine or corticotropin were less in the afternoon than in the morning. The relative amount of fall apparently depends upon the coincident direction of the spontaneous diurnal cycle as well as upon the health of the adrenocortical system.

The number of schizophrenics showing a fall of 50% or greater to epinephrine (13/30) or to corticotropin (18/30) in the morning was smaller than would be expected in a group of healthy men.

Of the 30 schizophrenics, 11 had been classified as catatonic and 12 as paranoid. The results in these two groups showed distinct differences.

The catatonics showed relatively normal responses to epinephrine and corticotropin but decreases greater than normal on the control morning. The paranoids produced significantly smaller responses to epinephrine and corticotropin but normal eosinophile changes in the control periods.

The mean absolute level of circulating eosinophiles in the catatonics was similar to that in normals, whereas that of the paranoids was twice as high.

It is concluded that these eosinophile studies provide presumptive evidence that the adrenocortical system is hypoactive and hyporeactive in the paranoid schizophrenic and perhaps hyperreactive in the catatonic schizophrenic. This may explain the conflicting reports on adrenocortical function in schizophrenia.

SPINAL CORD COMPRESSION STUDIES

I. Experimental Techniques to Produce Acute and Gradual Compression

I. M. TARLOV, M.D.

H. KLINGER, B.A.

AND

S. VITALE

NEW YORK

THERE IS much controversy over the proper treatment of acute and chronic spinal cord compression. Not everyone agrees, for instance, on the best time to operate in cases of acute compression of the spinal cord or cauda equina, or whether to operate at all.

Some of the signs and symptoms accompanying these lesions, moreover, are perplexing, and even misleading. Kahn [1] has called attention to the primary lateral sclerosis syndrome resulting from anterior spinal cord compression. Only recently, indeed, several well-known neurologists made a diagnosis of primary lateral sclerosis in a quadriplegic woman. At operation, however, one of us (I. M. T.) removed a ventrally placed meningioma from the cervical portion of her spinal cord. On occasion, also, "neoplasms may simulate subacute combined degeneration of the spinal cord." [2]

In an effort to throw light on these problems, we have submitted them to experimental analysis in laboratory animals. The project necessitated developing special techniques for producing acute and gradual compression of the spinal cord. This communication describes the structure and use of our equipment.

DEVICE FOR ACUTE COMPRESSION

This device, shown in Figure 1, is hydraulic in principle. Its essential parts are a metallic compressor unit and a compression unit, consisting of two rubber balloons —the larger one semicircular, the smaller bulb-shaped—connected by polyethylene and metallic tubes. The compressor unit has five parts, machined from stainless steel. When the compressing screw is tightened, the bottom flange moves up toward the middle flange, compressing the semicircular balloon and forcing fluid through the connecting tubes to the small balloon, which is thereby inflated.

From the Department of Neurology and Neurosurgery, New York Medical College, Flower and Fifth Avenue Hospital.

This study was aided by grants from the United States Public Health Service, the Veterans Administration, and the Dazian Foundation.

1. Kahn, E. A.: The Role of the Dentate Ligaments in Spinal Cord Compression and the Syndrome of Lateral Sclerosis, J. Neurosurg. **4**:191-199, 1947.

2. Oberhill, H.; Smith, R. A., and Bucy, P. C.: Neoplasms of Central Nervous System Simulating Degenerative Disease of Spinal Cord, J. A. M. A. **151**:612-619, 1953.

INSERTION OF DEVICE IN ANIMAL

A one-segment laminectomy is made several segments caudal to the site chosen for compression. The dura is exposed far laterally, to the ventral wall of the vertebral canal.

The top flange of the compressor unit is then fixed to the skin by forcing its female collar through a stab wound made several centimeters to one side of the laminectomy incision. The middle flange is then slipped under the skin and over this projecting female collar. A set screw in the middle flange is then tightened to secure it to the top flange. To prevent it from rotating when the compressing screw is tightened, the middle flange is fastened to the deep dermal layers with sutures passing through holes in the flange. The bottom flange is now threaded on the lower end of the compressing screw, which runs down from the top flange. The

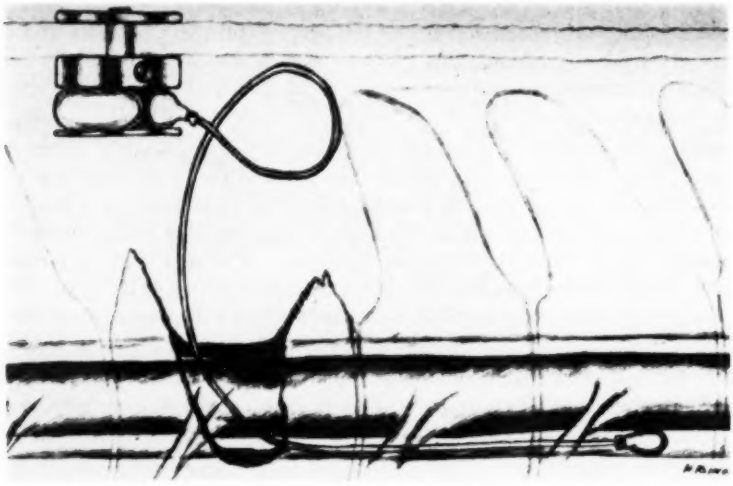

Fig. 1.—Drawing showing positions of compressor and compression units. Note the small balloon two vertebral segments above the laminectomy site.

semicircular balloon is now placed between the bottom and the middle flange, and the bulb-shaped balloon is gently pushed upward under the spinal cord to the desired level. The external surface of the compressor device is sealed with collodion.

Compression, begun after the animal's recovery from the operation, is done by tightening the compressing screw. Of course, the number of turns of the screw determines how much the bulb is inflated and the spinal cord compressed (Fig. 1), whether only partially or completely. During the compression the unanesthetized animal may be observed and examined and any loss or impairment of function studied.

Any degree of compression can be maintained for any length of time. Later, after decompression of the spinal cord (or cauda equina), it is possible to investigate recovery of function under various conditions. The metallic compressor device should be removed a day or two after decompression. If it is left longer, a rather intense inflammatory reaction sets in around it, and the skin between the top and

the middle flange is liable to become necrotic. The smaller balloon and the polyethylene tubes are allowed to remain in the spinal canal. Moderate inflammation and cicatricial reaction take place around this balloon, which, as a preventive measure, may easily be removed.

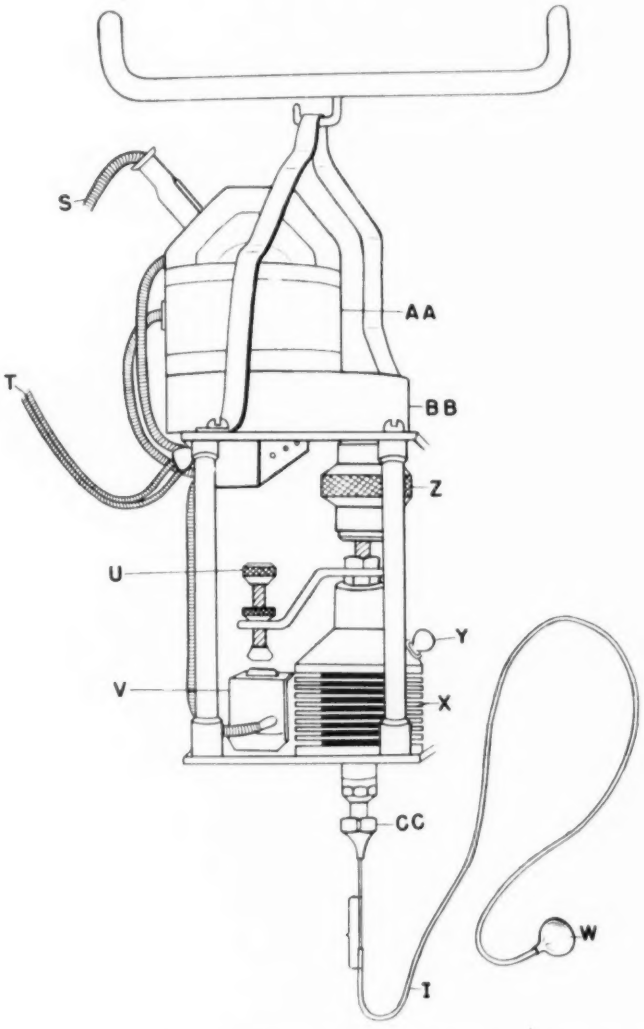

Fig. 2.—Drawing of gradual-compression device. The motor (*AA*) and the motor reduction gear race (*BB*) may be removed and replaced by others to increase or decrease the rate of compression.

CC indicates hypodermic needle; *I*, polyethylene tubing; *S*, wires to electric clock connected in parallel with motor so that the time of the motor shut-off can be read from the face of the stopped clock; *T*, wires to source of electric current; *U*, adjusting screw for switch cut-off; *V*, micro-cut-off switch; *W*, rubber balloon; *X*, flexible bronze bellows; *Y*, filling knob for bellows; *Z*, reset knob and compression screw.

DEVICE FOR GRADUAL COMPRESSION

This device consists essentially of a fixed-speed motor attached to a shaft that turns a screw compressing a bronze bellows (Fig. 2). The bellows forces water or, if roentgenographic control is desired, Thorotrast through connecting tubes into a bulb-shaped rubber balloon, like that used for acute compression.

A micromanometer is incorporated in the fluid system of this machine. From the pressure changes indicated on it while the machine is operating one may determine the size and volume of the balloon and whether there are leaks in the fluid system.

The pressure changes depend on the particular motor attached to the compressing machine, on the quantity of fluid in the hydraulic system, and on the particular

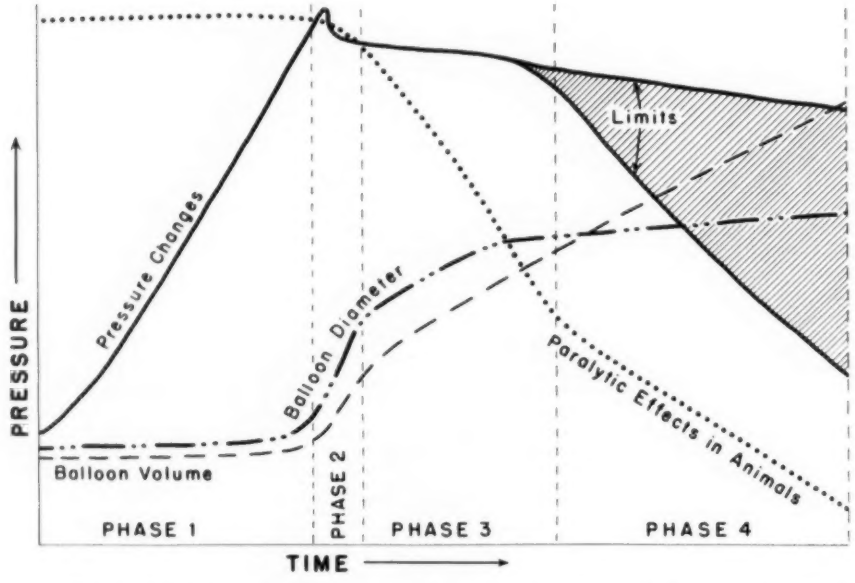

Fig. 3.—Balloon changes and paralytic effects occurring with gradual-compression machine.

balloon used. The balloon is the greatest source of variation in the pressure changes. We have been unable to produce balloons of uniform tensile strength and elasticity, so that the amount of pressure required to inflate them has varied. Nevertheless, we have found a characteristic course of inflation relative to the pressure changes in the hydraulic system. This is shown in the accompanying graph (Fig. 3).

The graph shows four phases in the inflation of the balloon. In the initial phase the pressure rises immediately after the machine is started. During this phase the volume and diameter of the balloon do not increase. When the pressure overcomes the resistance of the balloon rubber, the second phase, inflation, begins. The manometer indicates a slight, but rather rapid, drop in pressure during the second phase because of the sudden increase in volume and size of the balloon. During the third phase the pressure remains fairly constant, whereas the balloon steadily

increases in size. During the fourth phase the pressure declines as the balloon increases slowly in size. When the bellows contents are exhausted, the machine is automatically disconnected by the cut-off switch.

To set up the gradual compression machine, one should follow the following procedure: A hypodermic syringe filled with Thorotrast is connected to the tubing where the balloon is normally attached. The knurled knob driving the bellows screw is turned counterclockwise to its full limit. The bellows is thus fully opened. The Thorotrast is then injected until the bellows is filled to the top of the opening, which is then closed by the screw cap (*Y*). The injection is continued until the manometer registers a pressure of about 50 mm. of mercury. The tubing just above the syringe is bent sharply backward to seal the fluid in the system. The syringe is disconnected and the balloon is attached. The tubing is now straightened out and the fluid thus

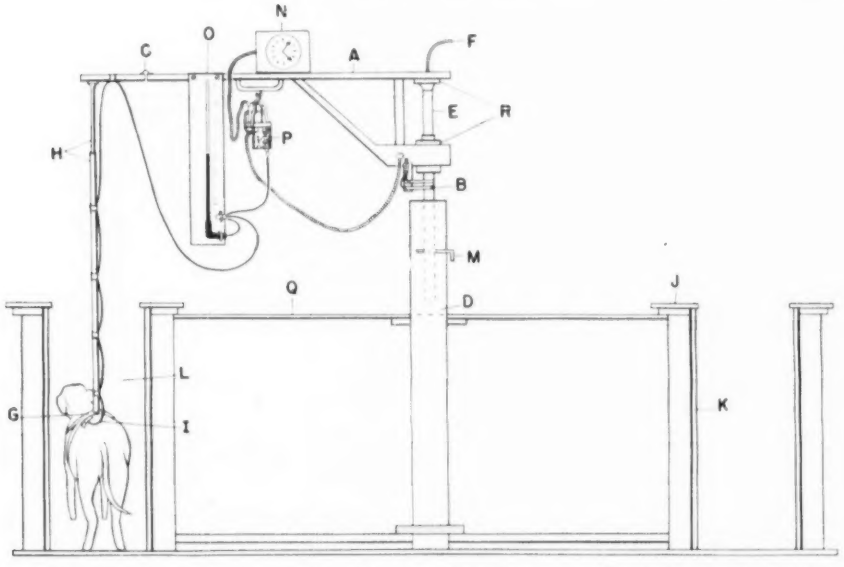

Fig. 4.—Drawing of sectional view of cage, guide, and compression device attached to dog. *A*, revolving arm with electrical outlet, gradual-compression device, electric clock, and manometer; *B*, commutator, conducting electric current from stationary source to revolving arm; *C*, hinged joint; *D*, supporting post in center of circular cage; *E*, stationery supporting shaft; *F*, plug to electric current; *G*, yoke; *H*, telescoping brass tubes to adjust height of yoke; *I*, polyethylene tubing attached to balloon within spinal column; *J*, protective railing, plywood cap; *K*, wire screening; *L*, space, allowing dog to move forward or backward only; *M*, locking pin, which keeps shaft stationary; *N*, electric clock; *O*, closed capillary mercury micromanometer connected with the compression unit through a T-tube running between bronze bellows and rubber balloon (12-in. [30 cm.] manometer, calibrated with a measured mercury column, can easily withstand the two atmospheres of pressure required to inflate the balloons to a diameter of approximately 1 cm.); *P*, compression unit; *Q*, braces supporting center post.

allowed to enter the balloon. If an excess of fluid has been forced into the system, the balloon will be inflated spontaneously. If so, the balloon must be disconnected, a small amount of fluid allowed to escape, and the balloon reconnected.

The manometer pressure is now recorded. The machine is turned on and tested for about an hour. A drop in the positive manometer pressure indicates a leak in the system.

The degree of the balloon inflation may now be determined in the following way: The bellows screw is turned slowly clockwise to compress the bellows. The pressure and the balloon diameter are determined at each one-eighth or one-quarter turn. The volume of the balloon can be calculated from its diameter: $V = \pi r^3$. The machine is allowed to stand with the balloon fully inflated for 30 minutes. Pressure often drops slightly during this time because the balloon rubber stretches as a result of its contained pressure.[3] The microswitch turn-off screw should now be checked to see that it has depressed the switch sufficiently to turn off the machine when the balloon has reached the desired size. The balloon may now be sterilized in a solution of benzalkonium (Zephiran) chloride. It is then ready for use in the animal.

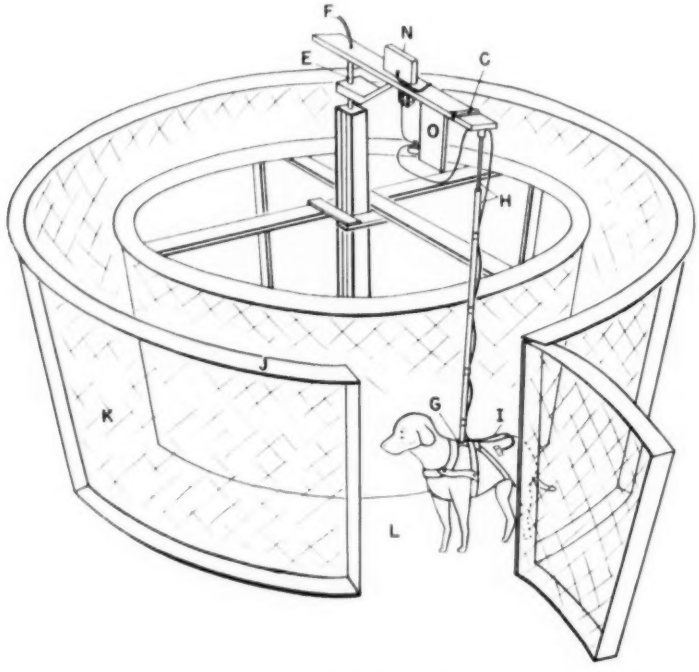

Fig. 5.—Drawing of perspective view of cage, guide, and attachments to dog.

The foregoing procedure makes it possible to determine the approximate size of the balloon at all times when it is in position in the animal and the machine in operation. The pressure readings are slightly higher when the balloon is in the spinal canal because of the counterpressure exerted within the spinal canal.

The graph shows that the inflation of the balloon is not linear, as would be most desirable. An attempt to achieve a linear graph by using other materials and designs (Fig. 3) is now being made.

The electric clock is used to indicate the exact time at which the cut-off switch disconnects the compression machine.

3. A marked drop in pressure, however, indicates a leak in the system.

In preparation for the in vivo experiment, the balloon is placed under the spinal cord, as for acute compression, and the polyethylene tube fixed to the skin with collodion. Compression is not begun, however, until the animal has recovered from the operation, which requires only a day or two or less.

When the animal has fully recovered, he is placed in the circular cage, which is just wide enough for him to move forward or backward (Figs. 4 and 5). He is then harnessed to the revolving guide, and compression of the spinal cord is begun. The guide does not interfere at any time with the observation of hind-limb function while sensory and motor paralysis is increasing.

Various motors may be used for compression, depending on the rate at which the investigator wishes the compressing screw to turn. The rate may be anywhere from one revolution a day to one a month, or even slower. Through gradual compression of the spinal cord (or cauda equina), with this device it is therefore possible to induce complete paralysis at the end of any desired time.

USES OF COMPRESSION TECHNIQUES

These techniques make it possible to determine the sequence of loss and recovery of function and to find out how long the spinal cord (or cauda equina) may be compressed before all function is permanently lost. Usual techniques [4] for testing a variety of sensory functions, such as pinprick appreciation and position and tactile senses, and motor power were used.

These devices can be used for the experimental study of the effect of compression of the brain and other organs. They can also be adapted to produce gradual occlusion of blood vessels in cases in which abrupt interruption of blood flow would be hazardous.

SUMMARY

We have developed techniques to produce acute and gradual compression of the spinal cord or cauda equina in unanesthetized animals. Many problems in clinical diagnosis and treatment and in spinal cord physiology can be studied with these new techniques.

4. Tarlov, I. M., and Bornstein, W.: Nerve Regeneration: A Comparative Experimental Study Following Suture by Clot and Thread, J. Neurosurg. **5**:62-83, 1948.

News and Comment

CONTINUATION COURSE IN NEUROLOGY, UNIVERSITY OF MINNESOTA

The University of Minnesota will present a continuation course in Neurology for General Physicians and Specialists from Jan. 25 to 30, 1954, in the Center for Continuation Study.

Diagnosis and management of the more commonly met neurological disorders will be stressed. The guest faculty will include Dr. Madison H. Thomas, chairman, neurology section, department of psychiatry, University of Utah College of Medicine; Dr. A. Theodore Steegman, professor and chief, department of neurology, University of Kansas Medical Center, and Dr. Adolph L. Sahs, professor and head, department of neurology, State University of Iowa College of Medicine. As an integral part of the course, the annual John B. Johnston lecture will be presented on the evening of Jan. 27 by Dr. Andrew T. Rasmussen, professor emeritus of anatomy, University of Minnesota Medical School. The course will be presented under the direction of Dr. A. B. Baker, professor and director of neurology, who will be joined by other members of the faculty of the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study.

CONTINUATION COURSE IN CHILD PSYCHIATRY, UNIVERSITY OF MINNESOTA

A continuation course in Child Psychiatry for General Physicians, Pediatricians, and Psychiatrists will be presented by the University of Minnesota Feb. 1 to 5, 1954. The course will consist principally of small-group discussions of common problems led by recognized experts in the field. A minimum of didactic lecture material will be presented. The guest faculty will include Dr. Sherman Little, director, orthopsychiatric department, Children's Hospital, Buffalo; Dr. Mabel Ross, Mental Health Consultant, United States Public Health Service, New York, and Dr. Henry H. Work, assistant professor of pediatrics and psychiatry, University of Louisville School of Medicine. The course will be presented under the direction of Dr. Reynold A. Jensen, professor, department of psychiatry and pediatrics, at the University of Minnesota Medical School. Lodging and meal accommodations are available at the Center for Continuation Study.

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